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HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For The Phthalate Esters Category

Prepared by:

ExxonMobil Biomedical Sciences, Inc.

For The

Phthalate Esters Panel, HPV Testing Group of the American Chemistry Council

December 18, 2006
(Revision to Test Plan Dated December 10, 2001)

LIST OF MEMBER COMPANIES
THE PHTHALATE ESTERS PANEL

The American Chemistry Council, Phthalate Esters Panel
is composed of the following member companies:

BASF Corporation
Eastman Chemical Company
ExxonMobil Chemical Company
Ferro Corporation
Teknor Apex Company

PHTHALATE ESTERS CATEGORY

CAS Number	CAS Number Description
Low Molecular Weight Phthalate Esters Subcategory	
131-11-3	1,2-benzenedicarboxylic acid, dimethyl ester (DMP)
84-66-2	1,2-benzenedicarboxylic acid, diethyl ester (DEP)
Transitional Phthalate Esters Subcategory	
68515-50-4	1,2,-benzenedicarboxylic acid, dihexyl ester, branched and linear (DHP)
68515-44-6	1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear (DinHP)
71888-89-6	1,2-benzenedicarboxylic acid, di-C6-8 branched alkyl ester, C7 rich (DIHP)
27554-26-3	1,2,-benzenedicarboxylic acid, diisooctyl ester (DIOP)
111381-89-6	1,2-benzenedicarboxylic acid (C7, C9) ester, branched and linear (79P)
111381-90-9	1,2-benzenedicarboxylic acid, (C7,C11) ester, branched and linear (711P)
16883-83-3	1,2-Benzenedicarboxylic acid, benzyl 3-hydroxy-1-isopropyl-2,2-dimethylpropyl ester isobutyrate (B84P)
High Molecular Weight Phthalate Esters Subcategory	
68648-93-1	1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters (610P)
117-84-0	1,2,-benzenedicarboxylic acid, dioctyl ester (DnOP)
68515-40-2	1,2-benzenedicarboxylic acid, benzyl C7-9 branched and linear alkyl esters (B79P)
68515-45-7	1,2,-benzenedicarboxylic acid, dinonyl ester, branched and linear (DNP)
68515-43-5	1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters (911P)
84-77-5	1,2-benzenedicarboxylic acid, didecyl ester (DDP)
3648-20-2	1,2-benzenedicarboxylic acid, diundecyl ester (DUP)
85507-79-5	1,2-benzenedicarboxylic acid, di (C11) ester, branched and linear (DinUP)
111381-91-0	1,2-benzenedicarboxylic acid (C9, C11) ester, branched and linear (Din911P)
68515-47-9	1,2,-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich (DTDP)

PLAIN ENGLISH SUMMARY

The proposed Phthalate Esters Category consists of nineteen phthalate esters. These substances are manufactured from 1,2-benzenedicarboxylic acids and alcohols, the latter of which range in carbon number from C_1 to C_{13}. The phthalate esters are divided into three subcategories based on their physicochemical and toxicological properties: Low Molecular Weight Phthalates, Transitional Phthalates, and High Molecular Weight Phthalates.

Low molecular weight phthalates are produced from alcohols with carbon (C) backbones $\leq C_3$. Two U.S. HPV (high production volume) chemicals, dimethyl and diethyl phthalate, are included in this subcategory. Low Molecular Weight Phthalates are commonly used as solvents or in cellulose acetate polymers. They have greater aqueous solubility and aquatic toxicity potential than the transitional phthalates, except for butyl benzyl phthalate (BBP), and high molecular weight phthalates. However, they have lower mammalian toxicity potential than the transitional phthalates.

Transitional phthalates are produced from alcohols with straight-chain carbon backbones that range from C4 to C6. One member is produced with a benzyl group. Seven U.S. HPV chemicals are included in this phthalate subcategory: dihexyl, diheptyl, diisoheptyl, diisooctyl, heptyl nonyl (C7/C9), heptyl undecyl (C7/C11), and a phthalate produced from benzyl alcohol as one ester group with the second ester group containing a C5 carbon backbone and butryate group. Transitional phthalates have lower water solubility than the low molecular weight phthalates and except for BBP, existing data suggest they do not exhibit acute or chronic aquatic toxicity. Transitional phthalates have varied uses from solvents to plasticizers for PVC. Some of these phthalates have greater mammalian toxicity potential, particularly with regard to reproductive and developmental effects, compared to either the low or high molecular weight phthalate categories.

High molecular weight phthalates are produced from alcohols with straight-chain carbon backbones $\geq$C7 or benzyl alcohol in conjunction with a diester group having a total carbon backbone $\geq$C7. Ten U.S. HPV chemicals fall into this subcategory, which includes phthalates containing linear and branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl, and ditridecyl alkyl groups. This subcategory also includes a phthalate with a benzyl group and a second group composed of a diester with combined alkyl groups totaling $\geq$C7. High molecular weight phthalates are used nearly exclusively as plasticizers of PVC. They are very insoluble in water, and have a very low vapor pressure. These substances have few biological effects.

The most common commercially available phthalate esters have been extensively studied for their potential toxicity. Existing toxicology data on the nineteen U.S. HPV phthalate esters were supplemented with published information on other phthalate esters currently being assessed under the OECD (Organization for Economic Co-operation and Development) SIDS (Screening Information Data Set) HPV Program (used as reference substances in the Phthalate Esters Category).

The ACC, Phthalate Esters Panel, HPV Testing Group believes that there is a sufficient amount of available data on phthalate esters to adequately characterize the human health effects, environmental fate and effects, and physicochemical endpoints for all members of the Phthalate Esters Category under the U.S. HPV Challenge Program. No additional testing is proposed for these materials.

EXECUTIVE SUMMARY

The American Chemistry Council (ACC), Phthalate Esters Panel, HPV Testing Group and its member companies hereby submit for review and public comment the test plan for the Phthalate Esters Category under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program (Program). It is the intent of the ACC Phthalate Esters Panel and its member companies to use existing data and scientific judgment/analyses to adequately characterize the SIDS (Screening Information Data Set) human health, environmental fate and effects, and physicochemical endpoints for this category.

This test plan addresses the 19 HPV phthalate esters listed in Table 1. Phthalate esters are produced by the reaction of phthalic anhydride with various linear and branched alcohols in the presence of an acid catalyst to form 1,2-benzenedicarboxylic acids. Benzyl alcohol is also used in some phthalate esters and one phthalate contains an isobutyrate ester at the terminal end of an alkyl group. The phthalate esters were subdivided into three subcategories based on their physicochemical and toxicological properties. The biological responses to phthalate esters vary based on the alcohol side group and the animal species tested. The proposed subcategories and test plan rationales are described below.

Table 1. CAS Numbers And CAS Descriptions Of Subcategory Members That Are HPV Chemicals.

CAS Number	CAS Number Description
Phthalates Subcategory 1 - Low Molecular Weight Phthalate Esters (<C3 backbone)	
131-11-3	1,2-benzenedicarboxylic acid, dimethyl ester (dimethyl phthalate, DMP)
84-66-2	1,2-benzenedicarboxylic acid, diethyl ester (diethyl phthalate, DEP)
Phthalates Subcategory 2 - Transitional Phthalate Esters (C4 to C6 backbone)	
68515-50-4	1,2,-benzenedicarboxylic acid, dihexyl ester, branched and linear (dihexyl phthalate, DHP)
71888-89-6	1,2-benzenedicarboxylic acid, di-C6-8 branched alkyl ester, C7 rich (diisoheptyl phthalate, DIHP)
68515-44-6	1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear (diheptyl phthalate, DinHP)
27554-26-3	1,2,-benzenedicarboxylic acid, diisooctyl ester (diisooctyl phthalate, DIOP)
111381-89-6	1,2-benzenedicarboxylic acid (C7, C9) ester, branched and linear (C7, C9 branched & linear, 79P)
111381-90-9	1,2-benzenedicarboxylic acid, (C7,C11) ester, branched and linear (C7,C11 branched & linear, 711P)
16883-83-3	1,2-Benzenedicarboxylic acid, benzyl 3-hydroxy-1-isopropyl-2,2-dimethylpropyl ester isobutyrate (B84P)
Phthalates Subcategory 3 - High Molecular Weight Phthalate Esters (≥C7 backbone)	
68648-93-1	1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters (610P)
117-84-0	1,2,-benzenedicarboxylic acid, dioctyl ester (dioctyl phthalate, DnOP)
68515-40-2	1,2-benzenedicarboxylic acid, benzyl C7-9 branched and linear alkyl esters (B79P)
68515-45-7	1,2,-benzenedicarboxylic acid, dinonyl ester, branched and linear (dinonyl phthalate, DNP)
68515-43-5	1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters (911P)
84-77-5	1,2-benzenedicarboxylic acid, didecyl ester (didecyl phthalate, DDP)
3648-20-2	1,2-benzenedicarboxylic acid, diundecyl ester (diundecyl phthalate, DUP)
85507-79-5	1,2-benzenedicarboxylic acid, di (C11) ester, branched and linear (diisoundecyl phthalate, DinUP)
111381-91-0	1,2-benzenedicarboxylic acid (C9, C11) ester, branched and linear (C9, C11 branched & linear, Din911P)
68515-47-9	1,2,-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich (di-tridecyl phthalate, DTDP)

Subcategories:

Low Molecular Weight Phthalate Esters: produced from alcohols with carbon (C) backbones $<C_3$. Two U.S. HPV chemicals, dimethyl phthalate (DMP) and diethyl phthalate (DEP), are included in this subcategory. The low molecular weight phthalates are distinguished from phthalates in other subcategories by use, physicochemical properties, and identified effects in toxicology studies.

Low molecular weight phthalates are commonly used as solvents or in cellulose acetate polymers rather than as plasticizers for PVC. Their higher volatility and water solubility give them physicochemical and toxicological properties different than the other phthalate esters in this category. In particular, these phthalates have greater aqueous solubility and aquatic toxicity potential than do the transitional phthalates, except for butyl benzyl phthalate (BBP), and high molecular weight phthalates. However, they have lower mammalian toxicity potential than the transitional phthalates.

Transitional Phthalate Esters: produced from alcohols with straight-chain carbon backbones of C4 to C6. This subcategory also includes a phthalate produced from benzyl alcohol as one ester group with the second ester composed of an alkyl group with a C5 carbon backbone and butyrate group. Phthalate esters containing $>10\%$ C4 to C6 molecules were conservatively included in this subcategory. Seven U.S. HPV chemicals are included in this subcategory: dihexyl, diheptyl, diisoheptyl, diisooctyl, heptyl/nonyl (C7/C9), heptyl/undecyl (C7/C11), and benzyl/isooctylbutyrate ester phthalates. Data for this subcategory were supplemented with published information on other phthalate esters (reference substances) currently being assessed under the OECD SIDS HPV and European Union Existing Substances Risk Assessment programs, including butylbenzyl phthalate (BBP), and di(2-ethylhexyl) phthalate (DEHP). Data from a structurally similar material, di-n hexyl phthalate (DnHP), were also included as read-across data to support the subcategory.

Transitional phthalates have varied uses, but are largely used as plasticizers for PVC. Physicochemical properties also vary in that the lower molecular weight transitional phthalates are more water-soluble than higher molecular weight transitional phthalates, but none would be characterized as highly water soluble. Transitional phthalates have lower water solubility than the low molecular weight phthalates and except for BBP, existing data suggest they do not exhibit acute or chronic aquatic toxicity. What distinguishes some of the transitional phthalates from others is their greater mammalian toxicity potential, particularly with regard to reproductive and developmental effects, compared to either the low or high molecular weight phthalate subcategories.

High Molecular Weight Phthalate Esters: produced from alcohols with straight-chain carbon backbones $\geq C7$ or benzyl alcohol in conjunction with a diester group having a total carbon backbone $\geq C7$. Ten U.S. HPV chemicals fall into this subcategory, which includes phthalates containing linear and branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl, and ditridecyl alkyl groups. Data for this subcategory were supplemented with published information on other phthalate esters (reference substances) currently being assessed under the OECD SIDS HPV or European Union Existing Substances Risk Assessment programs, including diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP). The category of phthalate esters reviewed by the OECD SIDS HPV program was referred to as the High Molecular Weight Phthalate Esters Category and included a number of phthalate esters in this subcategory. Results of studies on other non-HPV phthalates were included to supplement the database.

High molecular weight phthalates are used nearly exclusively as plasticizers of PVC. They are very poorly soluble in water, and have very low vapor pressure. The extant database demonstrates that these substances have few biological effects. A notable exception to this generalization is that hepatocarcinogenicity has been observed for DINP. The hepatocarcinogencity effects of DINP are by a mechanism (peroxisomal proliferation) to which rodents are particularly sensitive. However, it does not appear to be relevant to humans.

Testing Rationale:

Low Molecular Weight Phthalate Esters Subcategory

There is a large amount of data for the physicochemical properties of DMP and DEP. Computer models were also used to estimate these properties for comparison with select measured values and additionally were used to predict environmental distribution. No additional physicochemical studies are proposed for this subcategory.

Complete SIDS health effects data sets are available for DMP and DEP with the exception of reproductive data for DMP. However, data from DEP are used to characterize DMP reproductive toxicity. Both DMP and DEP show minimal acute toxicity, are not genotoxic, exhibit some liver and kidney effects at high doses, and are negative for developmental effects. Although the DMP database for reproductive effects is limited, the Panel believes that this endpoint can be adequately assessed by applying read-across data from DEP. Data on DEP indicate that this material will not cause reproductive effects. This is further supported by data showing that neither DEP nor DMP had effects on male reproductive development (Gray *et al.*, 2000). The lack of developmental effects observed with DMP, coupled with chronic toxicity studies showing no effects on reproductive organs (Lehman, 1955; NTP, 1995), negates the need to conduct a reproductive study for DMP. No additional toxicity studies are proposed for this subcategory.

There are several published acute and chronic aquatic toxicity studies in a variety of species of fish, invertebrates, and algae for DMP and DEP (Staples *et al.*, 1997a). No additional environmental toxicity studies are necessary.

Transitional Phthalate Esters Subcategory

There are measured and calculated physicochemical property data available for the transitional phthalates. Models were used to calculate physicochemical and select fate data for phthalates in this subcategory. The calculated data were developed from either a computer model used by the U.S. EPA, as cited in an EPA guidance document prepared for the HPV Challenge Program, or by published models developed using a training data set of measured data for phthalate esters. Depending upon the endpoint, the modeled data agree with measured data. The combination of measured values and calculated values is sufficient to provide the required information on the physiochemical and fate properties of the HPV phthalates in the transitional subcategory. No additional physicochemical studies are proposed for this subcategory.

A complete SIDS health effects data set is available for butyl benzyl phthalate (BBP). Although there is also a complete set of data available for diethylhexyl phthalate (DEHP), only the mammalian health data are used in this subcategory as additional supportive data. These substances are under review in Europe as part of the Existing Substances Risk Assessment program, and have been included as reference compounds in the transitional phthalate subcategory. Data on di-n-hexyl phthalate (non-HPV chemical) was also included to support read-across to dihexyl (branched and linear), diheptyl, and diisoheptyl phthalates. The available health effects data on other HPV chemicals in this subcategory are consistent with that reported for the above reference phthalates. Thus, studies from the reference compounds (BBP, DEHP, and di-n-hexyl (DnHP)) will be used as read-across data in conjunction with data from select transitional phthalates to predict the toxicity of the remaining untested members. No additional testing is proposed for this subcategory.

There is a full data set for environmental toxicity data on DHP, DEHP, DIOP, and 711P. In addition, there are also chronic fish toxicity data for DHP, DIHP, and 711P The lower molecular weight transitional phthalate, BBP, is more water soluble than the remaining higher molecular weight transitional phthalates (dihexyl and higher) and causes acute and chronic aquatic toxicity below 1 mg/L. There is an apparent cut-off in acute toxicity at dihexyl phthalate and higher; these results are further confirmed with QSAR modeling. Both calculated and measured values for environmental toxicity endpoints predict no effects at the limit of water solubility for dihexyl phthalate and higher. The data for the higher molecular weight transitional phthalates together with read-across data provide sufficient test data to suggest that these phthalates have no associated acute or chronic aquatic toxicity. No additional testing is proposed for this subcategory.

High Molecular Weight Phthalate Esters Subcategory

There are measured and calculated physicochemical property data available for the high molecular weight phthalates. Models were also used to calculate physicochemical and select fate data for phthalates in this subcategory. The calculated data were developed from either a computer model used by the EPA, as cited in an EPA guidance document prepared for the HPV Challenge Program, or by published models developed using a training data set of measured data for phthalate esters. Depending upon the endpoint, the modeled data agree with measured data. The combination of measured values and calculated values is sufficient to provide the required information on the physiochemical and fate properties of the HPV phthalates in the high molecular weight subcategory. No additional physicochemical studies are proposed for this subcategory.

A complete SIDS health effects data set is available for diisononyl (DINP) and diisodecyl (DIDP) phthalates. These substances were reviewed in Europe as part of the Existing Substances Risk Assessment, and have been included as reference compounds for the high molecular weight phthalate subcategory. Although not complete, health effects data are also available for many of the HPV substances in this subcategory. Additionally, a subset of the phthalates in this subcategory were reviewed under the OECD (Organization for Economic

Co-ordination and Development) SIDS HPV Program[1]. The conclusion agreed to by the member states and contained in the SIAP[2] follows:

> The chemicals possess properties indicating a low hazard for human health and the environment. Therefore, members of the HMWPE Subcategory are currently of low priority for further work because of their low hazard profile.

The high molecular weight phthalates all demonstrate minimal acute toxicity, are not genotoxic, exhibit some liver and kidney effects at high doses, and are negative for reproductive and developmental effects. Further, the available data indicate that the toxicological activity of these molecules diminishes with increasing molecular weight. The available data, supplemented with the data from the reference compounds DINP and DIDP, are sufficient to assess the toxicity of subcategory members with side groups in the C7 to C13 range. No additional testing is proposed for this subcategory.

Ecotoxicity test data in fish, invertebrates, and algae are available for most of the members of this subcategory and reference compounds. In addition, there are also chronic fish and invertebrate toxicity data for several of the members of this subcategory. These phthalates all contain side groups in the range of C7 to C13. All of the measured data for these higher phthalates show no effects from acute or chronic exposure to aquatic organisms. As with most of the members in the Transitional Phthalate subcategory, the higher molecular weight phthalates are too insoluble to exhibit acute or chronic toxicity. No additional testing is proposed for this subcategory.

[1] OECD (2004). High Molecular Weight Phthalate Esters (HMWPE) Subcategory. OECD HPV Program, Berlin, Germany.
[2] SIDS (Screening Information Data Set) Initial Assessment Profile

TEST PLAN FOR THE PHTHALATE ESTERS CATEGORY

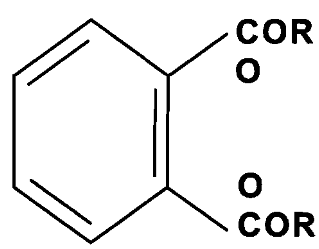
INTRODUCTION

The American Chemistry Council (ACC), Phthalate Esters Panel, HPV Testing Group and its member companies have committed voluntarily to provide screening level human health effects, environmental effects and fate, and physicochemical data for the phthalate esters category under the U.S. Environmental Protection Agency's (EPA's) High Production Volume (HPV) Challenge Program (Program).

This test plan identifies CAS numbers used to characterize the SIDS endpoints for this category, identifies existing data of adequate quality for substances included in the category, and provides the Panel's rationale for applying the available SIDS data to characterize the hazards of all category members. The objective of this effort is to identify and adequately characterize the physicochemical properties, human health, and environmental fate and effects in compliance with the U.S. EPA HPV Program.

DESCRIPTION OF THE PHTHALATE ESTERS CATEGORY

The phthalate esters comprise a family of chemicals synthesized by esterifying phthalic anhydride with various alcohols in the presence of an acid catalyst. The category includes the 19 HPV phthalate esters listed in Table 1. Phthalate esters in this category are all 1,2-benzenedicarboxylic acids esterified with side groups ranging from C_1 to approximately C_{13} (figure below). The structural formula for phthalate esters varies depending on the composition of the alcohols used in their manufacture. Alkyl side groups may be linear alkyl isomers (e.g., di-methyl and di-n-hexyl phthalates), branched alkyl isomers (e.g., diisohexyl phthalate), and/or a combination of benzyl and linear or branched isomers (e.g., benzyl butyl phthalate and benzyl C7-C9 branched and linear phthalate). One phthalate ester is also a combination of a benzyl group and a branched octyl butyrate ester group.



(R=side group)

Phthalate esters are generally clear to yellow, oily liquids with high boiling ranges ($\geq$250°C) and low vapor pressures; properties which contribute to their high physical stability. They are readily soluble in most organic solvents and miscible with alcohol, ether, and most oils. The aqueous solubility of phthalate esters is inversely related to their molecular weights. Lower molecular weight phthalates exhibit slight to moderate water solubility, whereas, higher molecular weight phthalates are poorly soluble.

The structural characteristics of the ester side groups affect both the physicochemical and biological properties of phthalate esters. The phthalate esters were subdivided into three subcategories based on their physicochemical and toxicological properties. The proposed subcategories are as follows:

Low Molecular Weight Phthalate Esters: produced from alcohols with carbon (C) backbones $<C_3$. Two U.S. HPV chemicals, dimethyl phthalate (DMP) and diethyl phthalate (DEP), are included in this subcategory.

Low molecular weight phthalates are commonly used as solvents or in cellulose acetate polymers rather than as plasticizers for PVC. Their relatively higher volatility and water solubility give them properties different than the other phthalate esters in this subcategory. In particular, these phthalates have greater aqueous solubility, resulting in a potential to cause acute and chronic toxic effects in aquatic organisms.

Transitional Phthalate Esters: produced from alcohols with straight-chain carbon backbones that range from C4 to C6. This subcategory also includes a phthalate produced from benzyl alcohol as one ester group with the second ester composed of an alkyl group with a C5 carbon backbone and butyrate group. Phthalate esters containing >10% C4 to C6 molecules were conservatively included in this subcategory. Seven U.S. HPV chemicals are included in this subcategory: dihexyl, diheptyl, diisoheptyl, diisooctyl, heptyl/nonyl (C7/C9), heptyl/undecyl (C7/C11), and benzyl/isooctylbutyrate ester phthalates. Data for this subcategory were supplemented with published information on other phthalate esters currently being assessed under the OECD SIDS HPV and European Union Existing Substances Risk Assessment programs, including butylbenzyl phthalate (BBP), and di(2-ethylhexyl) phthalate (DEHP). Data for a structurally similar material, di-n hexyl phthalate (DnHP), were also included as read-across data to support the subcategory.

Transitional phthalates have varied uses, but are largely used as plasticizers for PVC. Physicochemical properties also vary in that the lower molecular weight transitional phthalates are more water-soluble than high molecular weight transitional phthalates, but none would be considered to fall into the "high water soluble" subcategory. Transitional phthalates have lower water solubility than the low molecular weight phthalates and except for BBP, existing data suggest they do not exhibit acute or chronic aquatic toxicity. What distinguishes these phthalates from others is their greater mammalian toxicity potential, particularly with regard to reproductive and developmental effects compared to either the low or high molecular weight phthalate subcategories.

High Molecular Weight Phthalate Esters: produced from alcohols with straight-chain carbon backbones $\geq C7$ or benzyl alcohol in conjunction with a diester group having a total carbon backbone $\geq C7$. Ten U.S. HPV chemicals fall into this subcategory, which includes phthalates containing linear and branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl, and ditridecyl alkyl groups. Data for this subcategory were supplemented with published information on other phthalate esters currently being assessed under the OECD SIDS HPV or European Union Existing Substances Risk Assessment programs, including diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP). The category of phthalate esters reviewed by the OECD SIDS HPV program was referred to as the High Molecular Weight

Phthalate Esters Category and included a number of phthalate esters in this subcategory. Results of studies on other non-HPV phthalates were included to supplement the database.

High molecular weight phthalates are used nearly exclusively as plasticizers of PVC. They are very poorly soluble in water, and have a very low vapor pressure. The extant database demonstrates that these substances have few biological effects. A notable exception to this generalization is that hepatocarcinogenicity has been observed for DINP. The hepatocarcinogencity effects of DINP are by a mechanism (peroxisomal proliferation) to which rodents are particularly sensitive. However, it does not appear to be relevant to humans.

Substances were assigned to appropriate subcategories based on the composition of the ester side group structures (Table 2). In some cases the substances have ester side group constituents that span two subcategories (i.e., transitional and high molecular weight constituents). If the level of C4 to C6 constituents in the substance exceeded 10%, the substance was conservatively placed in the transitional subcategory.

Table 2. Typical Composition Ranges (Percent) For Substances In The Phthalate Esters Subcategory And Reference Substances.

Substance		Ester Side Chain Composition Range (%)			
CAS #	**Ester Group(s)**	**<C3**	**C4 to C6**	**≥C7**	**Benzyl Group**
Phthalates Subcategory 1 - Low MW Phthalates (<C3 ester backbone)					
131-11-3	Dimethyl	100			
84-66-2	Diethyl	100			
Phthalates Subcategory 2 - Transitional Phthalates (C4 to C6 ester backbone)					
85-68-7*	Butyl benzyl		50		50
68515-50-4	Dihexyl		100		
71888-89-6	Diisoheptyl		80	20	
117-81-7*	Diethylhexyl		100		
27554-26-3	Diisooctyl		70 to 75	<25	
68515-44-6	Diheptyl		30	70	
111381-89-6	C7, C9		15	85	
111381-90-9	C7, C11		15	85	
16883-83-3	Benzyl, C8C4		50		50
Phthalates Subcategory 3 - High MW Phthalates (≥C7 ester backbone)					
68648-93-1	C6, C8, C10		<1	99	
117-84-0	Dioctyl			100	
68515-40-2	Benzyl, C7 - C9		2	48	50
28553-12-0* 68515-48-0*	Diisononyl		5 to 10	>90	
68515-45-7	Dinonyl			100	
68515-43-5	C9 - C11			100	
84-77-5	Didecyl			100	
26761-40-0* 68515-49-1*	Diisodecyl			100	
111381-91-0	C9, C11			100	
3648-20-2	Diundecyl			100	
85507-79-5	Diisoundecyl			100	
68515-47-9 199-06-2	Diisotridecyl			100	

* HPV chemicals currently in the OECD SIDS HPV program. Data on these chemicals are being used for data read-across in appropriate subcategories.

DATA ADEQUACY REVIEW

<u>Literature Search:</u>

Literature searches were conducted by ExxonMobil Biomedical Sciences, Inc., Information Services on environmental and mammalian toxicity endpoints for 19 phthalate esters identified by the ACC, Phthalate Ester Panel, using CAS numbers only. Several comprehensive review articles on these chemicals have been published recently (Staples *et al.*, 1997a; Staples *et al.*, 1997b; Cousins and Mackay, 2000; David *et al.*, 2001). Therefore, the search was conducted using MEDLINE and TOXLINE databases and limited to studies published since 1995. In addition, the TSCATS database was searched for relevant unpublished studies on these chemicals. Standard handbooks, databases (Sax, CRC Handbook on Chemicals, IUCLID) and review articles were consulted for physicochemical properties.

An initial search of MEDLINE/TOXLINE conducted in May 2000 found ~150 records since 1994 that contained the CAS number and a toxicology term. A second search found >600 records since 1994 that contained a generic name and a toxicology term. This set was further reduced to ~70 records by requiring a name fragment and a toxicology term to be in the title. An additional 283 records were found in the TSCATS database.

Approximately 125 reports were selected for review based on the following criteria: relevant SIDS endpoint, relevant CAS number, final report of company study (TSCATS), peer reviewed journal, or comprehensive review article (e.g., Staples *et al.*; 1997b, David *et al.*, 2001; ATSDR review documents). With the exception of reports on dimethyl, diethyl, di C6-C8 branched, dioctyl, and diundecyl phthalate, very few publications on other phthalate esters were discovered in the literature search.

<u>Physicochemical Properties:</u>

As noted above, a few of the chemicals on the HPV list are the more common phthalates and several of these (dimethyl, diethyl, dihexyl, and dioctyl phthalates) are data rich. In these cases, there are a variety of literature values for physical properties. For a number of reasons, these values vary greatly. Literature reviews by Staples *et al.* (1997b) and Cousins and Mackay (2000) carefully evaluated the available values for these physical properties and selected representative values. The key data selected for robust summaries for these chemicals are the "best values" from the Staples *et al.* (1997a, 1997b) and Cousins and Mackay (2000) papers, based on a review of those data by scientists representing the various manufacturers.

In addition, modeled data were provided in robust summaries for all of the physical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/opptintr/chmrtk/robsumgd.htm) allows inclusion of calculated values described in robust summaries to characterize physicochemical elements
- The need for a complete set of physical property data in order to calculate environmental distribution
- The data gaps for physical properties for a few of these phthalates

The physical properties were modeled using the SRI/EPA computer program EPI Suite™ (2000), a modeling package that includes a number of algorithms developed at or for the EPA. EPI Suite™ is the program used and advocated by the EPA. Because the model is a structure-property model a specific discrete structure is required and EPI Suite™ contains a CAS number database which contains the structures for the chemicals. For mixtures, a single representative structure is contained in the database and in this work, these surrogate chemical structures were accepted for further modeling. It should be remembered that the resultant physical properties are for a single structure not a mixture so the values are discrete numbers rather than ranges.

Environmental Toxicity:

The environmental data selected for review were primarily obtained through a critique of the Environmental Toxicology and Chemistry review document Aquatic Toxicity of Eighteen Phthalate Esters, Staples *et al.* (1997). This comprehensive review document summarized the data of multiple species for all nineteen phthalates. From this list of studies, the following criteria were applied to those studies on phthalates matching the relevant CAS numbers.

a) Standard test species

b) Standard test endpoint or duration

c) Measured versus nominal values

d) Values representative of the data set presented

e) Exclusion of studies that were poorly conducted and reported values that were based on physical effects

Once a study was identified, a review of the study document was performed and a robust study summary prepared. A list of select environmental studies that were identified from the literature search but not selected for a robust summary, along with the reason why, is provided in **Appendix 1.**

Mammalian Toxicity:

The existing data for the mammalian toxicology endpoints were reviewed using the literature searches to identify the most relevant studies for each chemical in the category. A number of the individual chemicals on the list had no relevant studies identified in the searches. For the listed chemicals that contained relevant data, all available studies were reviewed using the criteria outlined in the EPA's methods for determining the adequacy of existing data for the HPV program and the ranking system proposed by Klimisch *et al.* (1997). A list of the most relevant studies that were available for the mammalian health endpoints is presented in **Appendix 1.**

Studies that were chosen for robust summaries represented the best available data for a particular SIDS endpoint. Published studies from the general literature, as well as a number of unpublished company reports, were obtained and summarized. Some endpoints include multiple study summaries in order to present a more complete data set. Some of the reported studies (particularly older acute data) could not be summarized because of insufficient experimental detail to assess their quality or because they were only reported as LD_{50} values in secondary sources. These studies are included in the data table (Table 3 (Attachment 1)) as supplementary information.

Some phthalate esters can be described by more than one CAS number (e.g., DINP, DIDP) and/or are relevant to several different phthalates (e.g., 711P). In these cases, the robust summary was provided on the most relevant CAS number but cross referenced to other applicable CAS numbers in both the robust summary and the data table (Table 3 (Attachment 1)).

One commercial test substance, 711P, is actually an equal composition mixture of six phthalate esters consisting of C7, C9, and C11 ester side chains. This test substance is considered by EPA under the following CAS nos.: 68515-44-6 (di-C7), 68515-45-7 (di-C9), 3648-20-2 (di-C11), 111381-89-6 (C7/C9), 111381-90-9 (C7/C11), and 111381-91-0 (C9/C11). With the exception of 111381-90-9 (C7/C11), each of these substances is also commercially sold as a separate product. The overall content of C4 to C6 isomers in 711P is approximately 10%, based on the contribution from branched C7 isomers e.g., di-C7 (30% C4 to C6); C7/C9 (15% C4 to C6); and C7/C11 (15% C4 to C6). Test data on 711P were used selectively as read-across data to all substances in the mixture based on the C4 to C6 content of each substance in the mixture. Phthalate esters with >10% C4 to C6 isomers were conservatively placed in the transitional subcategory. Diisooctyl phthalate ester (CAS # 27554-26-3) was also included in the transitional subcategory because this substance can contain >10% C6 isomers as dimethyl hexyl, although the EPI Suite™ model illustrates the structure as containing two methyl heptyl alkyl groups.

TESTING RATIONALE

Low Molecular Weight Phthalate Esters Subcategory ($\leq$C3)

<u>Overview:</u>

Low molecular weight phthalates are produced from alcohols with carbon backbones $\leq C_3$. The U.S. HPV chemicals, dimethyl (DMP) and diethyl (DEP) phthalate ester, are included in this subcategory. These phthalates are commonly used as solvents or in cellulose acetate polymers. The extant database on DMP and DEP is sufficient to adequately characterize their potential health and environmental effects. They have greater aqueous solubility and aquatic toxicity potential than do the transitional phthalates, except for BBP, and high molecular weight phthalates. However, they have lower mammalian toxicity potential than do the transitional phthalates.

A summary of the available toxicology and biodegradation data for this subcategory is shown in Table 3 (Attachment 1). Physicochemical properties and environmental fate information (other than biodegradation data) is provided in Table 4 (Attachment 2). A summary of the adequacy of the toxicology and biodegradation data and where read-across is applied is shown in Tables 5 and 6. No additional testing is proposed for this subcategory.

Table 5. Adequacy Of The Mammalian Toxicology Data For The Low Molecular Weight Phthalates.

	Acute	Repeat dose	Genetox (mut.)	Genetox (gene.)	Repro.	Develop.
DMP	A	A	A	A	r	A
DEP	A	A	A	A	A	A

A =adequate data
r =characterized from read-across data

Table 6. Adequacy Of The Environmental Toxicology And Biodegradation Data For The Low Molecular Weight Phthalates.

	Acute fish	Acute daphnid	Alga	Chronic fish	Chronic daphnid	Biodeg.
DMP	A	A	A	A	A	A
DEP	A	A	A	r	A	A

A =adequate data
r =characterized from read-across data

Physicochemical Properties:

There is a large amount of data for the physicochemical properties of DMP and DEP (Table 2). Computer models were also used to estimate these properties for comparison with measured values and additionally were used to predict environmental distribution. The calculated data were developed from a computer model used by the EPA, as cited in an EPA guidance document prepared for the HPV Challenge Program (U.S. EPA, 2000). Sufficient physicochemical data exist for all members of this subcategory and no further testing is necessary.

Mammalian Toxicity:

Acute Toxicity. DMP and DEP exhibit low acute toxicity by oral, dermal and inhalation routes of exposure. Although acute oral toxicity data on DEP are based on older, inadequate studies by current guidelines, the lack of lethality at doses ≥ 5 g/kg/day is consistent with that seen with other phthalate esters and subchronic studies on DEP.

Repeated Dose Toxicity. High dietary doses (5% or ~3,750 mg/kg/day) of DEP resulted in decreased body weights and tissue weights; no effects were seen in males at 1% (~750 mg/kg/day) or in females at 0.2 % (~150 mg/kg/day). These results are similar to that seen following dermal administration of DMP to rabbits for 90 days at 4g/kg/day. Neither DMP nor DEP exhibited chronic toxicity or carcinogenic effects in a one-year dermal initiation-promotion study in male mice (NTP, 1995). Further, no adverse effects were reported in rats fed diets containing up to 2% DMP for two years (Lehman, 1955).

Genetic Toxicity (Salmonella). Both DMP and DEP are negative for mutagenicity in the Ames assay (NTP, 1995). As all of these substances were inactive in these assays, no further testing of substances for point mutations is warranted.

Chromosomal Aberrations. Both DMP and DEP are negative for chromosomal damage in CHO cells *in vitro*. DMP was active in mouse lymphoma assay in the presence but not in the absence of S9 (Barber *et al.*, 2000); however, the overall weight of evidence from numerous genotoxicity assays indicates a lack of genotoxic effects (NTP, 1995).

Toxicity to Reproduction. No effects were seen in a two-generation reproductive study in mice fed DEP at doses of 3.2 g/kg/day. Although adequate reproductive studies are not available for DMP, data on DEP indicate that this material will not cause reproductive effects. This is supported by data showing that neither DEP or DMP had effects on male reproductive development (Gray *et al.*, 2000). Although study details are lacking, no adverse effects on reproductive organs were reported in chronic studies conducted on DMP (Lehman, 1955; NTP, 1995). The lack of developmental effects observed with DMP, coupled with chronic toxicity studies showing no effects on reproductive organs, negates the need to conduct a reproductive study for DMP.

Developmental Toxicity/Teratogenicity. No developmental effects have been observed following dietary exposure to either DMP or DEP at doses up to 5% (~3.2 g/kg) in rats.

Environmental Toxicity:

There are numerous published acute aquatic toxicity studies in a variety of species of fish, daphnia and algae for DMP and DEP (Staples *et al.*, 1997a). DMP and DEP are slightly soluble in aqueous systems. Acute effects on aquatic species are seen in the 10 to 150 mg/L range. Chronic effects are seen at levels >1 mg/L. No additional environmental toxicity studies are necessary.

Transitional Phthalate Esters Subcategory (C4-C6)

Overview:

As described elsewhere, there are seven phthalate esters in this subcategory. The substances in this subcategory have branched or linear side chains with a total carbon number ranging from C4 to C8 (this includes the linear portion and alky branching as opposed to just the linear portion). This subcategory also includes a phthalate produced from benzyl alcohol as one ester group with the second ester composed of an alkyl group with a C5 carbon backbone and butyrate group. The chemical property that distinguishes this subcategory of substances is that a predominant fraction of the alkyl side chains have linear portions with carbon numbers ranging from C4 to C6. Contained within this subcategory are substances with either linear or branched side chains, again with the stipulation that the branched molecules have a linear portion containing at least 4 but not more than 6 carbons. Some substances are predominantly linear; some predominantly branched; some with side chains of a single carbon number; and some with side chains covering a range of carbon numbers (e.g., di C6-C8 branched). Phthalate esters containing >10% C4 to C6 molecules were conservatively included in this subcategory. The grouping of these substances into a single subcategory is also justified on toxicological grounds as described below.

The substances in this subcategory which have been most extensively tested are butyl benzyl (BBP) and di-ethylhexyl phthalate (DEHP). These substances are under review in Europe as part of the Existing Substances Risk Assessment process, and, as a consequence, are already within the OECD SIDS process. BBP is included in this summary for reference purposes. The European risk assessment for DEHP, as well as the evaluation of the data at the OECD level, is now in its final draft form and is expected to be agreed by European Union Member States in 2006. Mammalian health data for DEHP are used in this subcategory as additional supportive data. There are several other phthalates including di-n-hexyl phthalate (DnHP, 84-75-3) which are not high volume substances but nevertheless provide data useful for assessing this subcategory of substances.

The data from the reference substances and other tested substances cover the majority of the carbon numbers and molecular types found in this subcategory. Thus, it is reasonable to assume that the data from the extensively tested members of this subcategory can be used to reasonably predict the toxicological properties of the less well studied members. With regard to aquatic toxicity for subcategory members with side groups containing greater or equal to six carbons, linearity or branching within the alkyl group will not affect the lack of aquatic toxicity exhibited by these members as the lack of toxicity is caused by their low water solubility and not side group structure.

A summary of the available toxicology data for this subcategory is shown in Table 3 (Attachment 1) and a summary of the adequacy of those data and where read-across is applied is shown in Tables 7 and 8. Physicochemical properties and environmental fate information is provided in Table 4 (Attachment 2). No additional testing is proposed for this subcategory.

Table 7. Adequacy Of The Mammalian Toxicology Data For The Transitional Molecular Weight Phthalates.

	Acute	Repeat dose	Genetox (mut.)	Genetox (gene.)	Repro.	Develop.
BBP*	A	A	A	A	A	A
DHP	r	A	r	A	r	r
DnHP*	A	A	A	-	A	A
DEHP*	A	A	A	A	A	A
Diheptyl	r	r	r	r	r	r
Diiso-heptyl	A	r	A	A	r	A
DIOP	r	r	A	A	r	r
C7, C9	r	r	A	A	r	A
C7, C11	r	r	A	A	r	A
Benzyl C8-oxybutyl	A	r	A	r	r	r

* Not a U.S. HPV chemical; included as read-across data to other subcategory members
A =adequate data
r =characterized from read-across data
- =not available or not needed as read-across data to support the subcategory

Table 8. Adequacy Of The Environmental Toxicology And Biodegradation Data For The Transitional Molecular Weight Phthalates.

	Acute fish	Acute daphnid	Alga	Chronic fish	Chronic daphnid	Biodeg.
BBP*	A	A	A	A	A	A
DHP	A	A	A	A	nd	A
DnHP*	r	r	r	r	nd	r
Diiso-heptyl	A	r	r	A	A	A
DEHP*	A	A	A	A	A	A
Diheptyl	r	r	r	r	r	r
DIOP	A	A	A	r	r	A
C7, C9	r	r	r	r	r	r
C7, C11	A	A	A	A	r	r
Benzyl C8-oxybutyl	A	r	A	r	r	r

* Not a U.S. HPV chemical; included as read-across data to other subcategory members
A =adequate data
nd =no data or equivocal data
r =characterized from read-across data
\- =not available or not needed as read-across data to support the subcategory

__Physicochemical Properties:__

Melting point and boiling point data are available for all of the members of this subcategory from Staples *et al.* (1997) or handbooks, except for diisoheptyl and benzyl/isooctylbutyrate phthalates. All of the phthalates higher than DMP have melting points below 0°C. DEP has a boiling point of 295°C and all data for higher phthalates have boiling points >300°C. Thus, there is sufficient evidence that diisoheptyl and benzyl/isooctylbutyrate phthalates would have melting points <0°C and boiling points >300°C. The melting points calculated by the EPI Suite™ program agree poorly (too high) with measured values for the phthalates.

Cousins and Mackay have tabulated and analyzed all of the measured water solubility, vapor pressure, and partition coefficient (K_{ow}) for all of the transitional phthalate esters, except for the C7, C9 phthalate (CAS# 111381-89-6) and benzyl/isooctylbutyrate phthalate (CAS# 16883-83-3). They have used correlations with molar volume and fugacity considerations to select the best values for dihexyl, diisohexyl, diheptyl, diisoheptyl, and diisooctyl phthalates. These values are considered the best values for water solubility, vapor pressure, and partitioning of these phthalates. These values also are in relatively good agreement with calculated values.

Hydrolysis half lives and atmospheric photodegradation rates are calculated by EPI Suite^{TM}. Phthalate ester hydrolysis rates are quite low and not a significant fate route. Environmental distribution was modeled by the EQC model, Levels I and III.

No measurements of the physicochemical or fate properties of this subcategory is necessary.

Mammalian Toxicity:

Acute Toxicity. The available data on phthalates spanning the carbon range from C4 to C6 indicate that phthalate esters in the transitional subcategory are minimally toxic by acute oral and dermal administration. The oral LD50 value for BBP exceeds 2 g/kg (NTP, 1982), and for materials with higher molecular weights, the LD50 values exceed the maximum amounts which can be administered to the animals in a manner consistent with the principles of responsible animal use. Some of these data have already been published (e.g., Krauskopf, 1973; Lawrence *et al.*, 1975), but there is also a substantial body of unpublished data. One member of this subcategory, DEHP, has been tested for acute inhalation toxicity. It did not cause an effect at the highest concentration tested. Further, considering the low volatility of these substances, inhalation exposure at toxicologically significant levels is not anticipated. Thus, further testing of substances in this subcategory for acute toxicity is not proposed.

Repeated Dose Toxicity. Several substances in the C4 to C6 range, including BBP, have been tested for repeated dose toxicity in studies ranging from 3 weeks to 2 years (e.g., Barber *et al.*, 1987; David *et al.*, 1999; 2000; 2001; NTP, 1982). The principal effects found in these studies were those associated with peroxisome proliferation including liver enlargement and induction of peroxisomal enzymes. As shown in a comparative study of liver effects (Barber *et al.*, 1987), the strongest inducers of peroxisome proliferation are DINP and DIDP with substances of shorter chain length (e.g., BBP) showing much less pronounced effects. Thus it is reasonable to conclude that other members of this subcategory would show effects similar to BBP and less pronounced than DINP or DIDP. It should also be noted that the relevance of these findings to human health is, at best, questionable. It has been shown that these effects are mediated through the peroxisome proliferation-activated receptor alpha (PPARα; Ward *et al.*, 1998) and that levels of PPARα are much higher in rodents than they are in humans (Tugwood *et al.*, 1996; Palmer *et al.*, 1998). Thus one would expect humans to be substantially less responsive than rodents to peroxisome proliferating agents. Empirical evidence that this is true is provided by studies in primates in which repeated administration of DINP (Hall *et al.*, 1999; Kurata *et al.*, 1998; Pugh *et al.*, 2000) had no effects on liver, kidney or testicular parameters.

Several of the substances in the transitional phthalate esters subcategory, however, have been shown to produce testicular atrophy when given to juvenile rats at high levels. Testicular atrophy has been associated with BBP (Lington *et al.*, 1993) and other substances with C4 to C6 linear carbon chains (Foster *et al.*, 1980). However, molecules with fewer than 4 or more than 6 carbons did not produce testicular atrophy in these studies (Foster *et al.*, 1980; Lington *et al.*, 1993). Although the relevance of these data are uncertain as the testes is not a target organ for DEHP in primates (Kurata *et al.*, 1998; Pugh *et al.*, 2000), these data do provide one of the distinguishing toxicological characteristics of this subcategory and are one of the underlying reasons supporting the differentiation of phthalate esters on the basis of length of the linear region of the carbon chain.

In summary, there is no need for further repeated dose studies of transitional phthalate esters in rodents. The effects in rodents have been well described for a number of representatives of this subcategory. The most sensitive indicators of effect are in the liver and associated with peroxisomal proliferation. The relevance of these effects to humans is questionable.

Genetic Toxicity (Salmonella). A number of the substances in this subcategory including the reference substance BBP has been assessed in the Salmonella (Zeiger *et al.*, 1985) and mouse lymphoma (Barber *et al.* 2000) assays. As all of these substances were inactive in these assays, no further testing of substances in the transitional phthalate esters subcategory for point mutations is warranted.

Chromosomal Aberrations. BBP and DHP were inactive in micronucleus assays in mice. DEHP was inactive in a cytogenetics assay in rat bone marrow. Diisoheptyl phthalate was inactive in CHO cells, in vitro. As substances spanning the range of materials in this subcategory have been tested in the standard assays for chromosomal aberration and found to be inactive, no further testing of chromosome aberration is warranted for transitional phthalate esters.

Toxicity to Reproduction. Robust summaries for reproductive and developmental effects of DEHP have been provided as part of the diisooctyl dossier in order to support the data within this subcategory. A series of studies assessed the structure-activity relationship of the effects of phthalate esters on fertility using a continuous breeding protocol (Lamb *et al.*, 1987; Heindel *et al.*, 1989). The test substances included in these studies were diethyl-, dipropyl-, dibutyl-, dipentyl-, d-n-hexyl-, di-2(ethylhexyl)-, and di-n-octyl phthalates. The most profound effects were on fertility (i.e., number of females delivering/number mated) and number of live births. The substance showing the greatest activity was DEHP which produced effects at dietary levels of 0.1% with a no effect level of 0.01%. The next most active compounds were di-n-hexyl- and di-n-pentyl phthalate which showed effects in the range of 0.3 to 0.5%; no effect levels were not experimentally defined. Dipropyl phthalate had an effect on live birth index at 2.5% but produced no effects at 1.25%. Diethyl phthalate and di-n-octyl phthalate were inactive at the highest levels tested, 2.5% and 5.0%, respectively. These data demonstrated that molecules with linear alkyl chains of 4 to 6 carbons profoundly affect fertility in rodents, with DEHP being the most active. Molecules with longer or shorter side chains are essentially inactive in these assays. These data were also a basis for the separation of phthalates into three categories based on length of side chain.

In addition to these data there are reproductive toxicity studies on BBP (Nagao *et al.*, 2000; Tyl, 2004) and DEHP (Schilling *et al.*, 1999). Additional work on BBP and DEHP is ongoing. A recent 2-generation reproductive study was conducted in rats in which BBP was administered via the diet. Parental effects were limited to changes in body weight, weight gain, and increased absolute and relative liver weights. In the F1 parents, treatment with BBP affected mating and fertility indices and sperm number and motility. The F1 male offspring exhibited shortened anogenital distance, delayed acquisition of puberty and retention of nipples and areolae as well as reproductive effects. The NOAEL of the study was reported to be 3750 mg/kg for reproductive effects. However, for male F1 and F2 offspring, the NOEL for reproductive effects was reported to be 50 mg/kg based on reductions in anogenital distance. These studies along with previous data provide a good basis to assess the reproductive effects of C4 to C6 phthalate esters. Although several substances (diheptyl, heptyl nonyl, heptyl undecyl) have ester side chain constituents that predominately fall in the high molecular weight subcategory, these substances are conservatively assumed to exhibit reproductive effects similar to other transitional phthalates. In light of recent data, there will be no need for further reproductive toxicity studies of substances in this subcategory.

Developmental Toxicity/Teratogenicity. There have been extensive studies of the developmental toxicity of BBP and DEHP (NTP, 2000). These substances produce structural malformations and also affect male reproductive development. No effect levels are in the range of 50 to 300 mg/kg bw/day. There is also an unpublished developmental toxicity study of di-isoheptyl phthalate (DIHP). The results of these studies are broadly consistent with the structure-activity relationships previously described, i.e., that phthalate esters with linear carbon chains of C4 to C6 carbons produce much more profound effects that either shorter or longer molecules.

Phthalate esters with >10% C4 to C6 isomers were conservatively placed in the transitional subcategory. This conclusion is supported by developmental test data on 711P, which showed structural malformations in rats at 1000 mg/kg day with a NOAEL of 200 mg/kg/day (Hellwig *et al.*, 1997). As previously discussed, 711P is an equal composition mixture of six phthalate esters consisting of linear and methyl-branched C7, C9, and C11 ester side chains. This test substance is considered by EPA under the following CAS nos.: 68515-44-6 (di C7), 68515-45-7 (di C9), 3648-20-2 (di C11), 111381-89-6 (C7, C9), 111381-90-9 (C7, C11), and 111381-91-0 (C9, C11). The overall content of C4 to C6 isomers in 711P is approximately 10%, based on the contribution from methyl-branched C7 isomers e.g., di C7 (30% C4-C6); C7, C9 (15% C4-C6); and C7, C11 (15% C4-C6). Test data on 711P were used selectively as read-across data to the C7-containing substances in the mixture, based on the C4 to C6 content of each substance in the mixture.

The available data permit an assessment of the developmental toxicity of this subcategory of products, and no further testing of individual members is warranted.

Environmental Toxicity:

There is a full data set for aquatic toxicity data of dihexyl, diisooctyl, and 711P phthalates in fish, invertebrates, and algae. These data were supplemented with a full environmental data set on BBP. Although BBP causes acute and chronic aquatic toxicity, the existing data for the next lowest molecular weight phthalate in this subcategory suggest that dihexyl phthalate causes no acute and chronic effect at its maximum water solubility (Staples *et al.*, 1997a). This cut-off in acute toxicity is due to the concentration causing acute toxicity being higher than the water solubility of the phthalate ester, as was elegantly shown by Parkerton and Konkel (2000). The same situation exists for those phthalates which are more non-polar (higher carbon number) than dihexyl phthalate. This is confirmed by a lack of acute toxicity to fish, invertebrates, or algae for DHP, DIHP, DIOP, 711P, and B84P (Staples *et al.*, 1997a). These results are further confirmed with QSAR modeling. Thus, read across data for the other transitional phthalates, together with a phthalate specific aquatic toxicity QSAR (Parkerton and Konkel, 2000), leads to the conclusion that the other members of this subcategory will not cause acute aquatic toxicity. Additionally, chronic fish toxicity data for DHP, DIHP, and 711P, and chronic daphnia toxicity data for DIHP show that phthalate esters within this subcategory (except for BBP) cause no chronic effects. BBP causes acute and chronic toxicity at levels below 1 mg/L. As a consequence, no further aquatic toxicity testing is necessary.

High Molecular Weight Phthalate Esters Subcategory ($\geq$ C7)

__Overview:__

As described elsewhere, there are ten phthalate esters in this subcategory. The substances in this subcategory have branched or linear side chains with carbon numbers ranging from C7 to C13. The distinguishing chemical property for this subcategory of substances is that a predominant fraction of the alkyl side chains have linear portions containing at least 7 carbons. Contained within this subcategory are substances with either linear or branched side chains, again with the stipulation that the branched molecules must have a linear portion of at least 7 carbons. Some substances are predominantly linear; some predominantly branched; some with side chains of a single carbon number; and some with side chains covering a range of carbon numbers (e.g., C7-C9 phthalate). In some cases the substances have a small fraction of smaller constituents (e.g., 610P), but if the level of such constituents exceeded 10%, the substance was placed in the lower (i.e., C4-C6) transitional subcategory. The grouping of these substances in a single subcategory is also justified on toxicological grounds as described below.

Among the substances which have been most extensively tested in this subcategory are DINP (CAS # 28553-12-0, CAS # 68515-48-0) and DIDP (CAS # 26761-40-0 and CAS # 68515-49-1). Both of these substances have been reviewed in Europe as part of the Existing Substances Risk Assessment Process, and as a consequence are already within the SIDS review process. They are included in this review for reference purposes and to support the subcategory as a whole. The risk assessment of these substances as well as the evaluation of the data at the OECD level has been completed. There are several other substances including C7-C9 phthalate (CAS # 68515-41-3) and ditridecyl phthalate (CAS # 119-06-2) which are not high volume substances, but nevertheless also provide data useful for assessing this subcategory.

Included among the substances in this subcategory that are not undergoing evaluation for purposes of the U.S. HPV Program are DnOP, DUP, benzyl C7-9, C9-C11, and DTDP. The data from these substances and those in the HPV Program cover the majority of carbon numbers and molecular types found within this subcategory. Thus, it is reasonable to assume that the data from the extensively tested members of this subcategory can be used to reasonably predict the toxicological properties of the less studied members. Specifically, health effects data are not presented for 610P, didecyl phthalate, and DIUP. For these phthalates, the C6 (CAS # 117-81-7), C8 (CAS # 117-84-0), and C7-C11 (CAS # 26761-40-0; CAS# 68515-49-1) phthalates are considered appropriate sources for read across. With regard to aquatic toxicity for subcategory members with side groups containing greater or equal to six carbons, linearity or branching within the alkyl group will not affect the lack of aquatic toxicity exhibited by these members as the lack of toxicity is caused by their low water solubility.

A summary of the available toxicology data for this subcategory is shown in Table 3 (Attachment 1) and a summary of the adequacy of those data and where read-across is applied is shown in Tables 9 and 10. Physicochemical properties and environmental fate information is provided in Table 4 (Attachment 2). No additional testing is proposed for this subcategory.

Table 9. Adequacy Of The Mammalian Toxicology Data For The High Molecular Weight Phthalates.

	Acute	Repeat dose	Genetox (mut.)	Genetox (gene.)	Repro.	Develop.
610P	r	r	r	r	r	r
DnOP	A	A	A	r	A	A
Benzyl C7-9	A	r	A	r	r	r
C7-9*	A	A	A	r	A	A
DINP*	A	A	A	A	A	A
Dinonyl	r	r	r	r	r	r
C9-11	r	r	r	r	A	A
Didecyl	r	r	r	r	r	r
DIDP*	A	A	A	A	A	A
DUP	A	A	A	r	r	r
DIUP	r	r	r	r	r	r
C9, C11	r	r	r	r	r	r
DTDP	A	r	A	r	r	r
C13*	A	A	A	A	A	A

* Not a U.S. HPV chemical; included as read-across data to other subcategory members
A =adequate data
r =characterized from read-across data
- =not available or not needed as read-across data to support the subcategory

Table 10. Adequacy Of The Environmental Toxicology And Biodegradation Data For The High Molecular Weight Phthalates.

	Acute fish	Acute daphnid	Alga	Chronic fish	Chronic daphnid	Biodeg.
610P	A	A	A	r	r	A
DnOP	r	r	r	r	r	A
Benzyl C7-9	A	r	r	r	r	r
C7-9*	A	A	r	r	A	r
DINP*	A	A	A	A	A	A
Dinonyl	r	r	r	r	r	r
C9-11	r	r	r	r	r	r
Didecyl	r	r	r	r	r	r
DIDP*	A	A	A	A	A	A
DUP	A	A	A	r	A	A
DIUP	r	r	r	r	r	r
C9, C11	r	r	r	r	r	r
DTDP	A	A	A	r	A	A

A =adequate data
r =characterized from read-across data
- =not available or not needed as read-across data to support the subcategory

Physicochemical Properties:

Melting points and boiling points are generally available for the phthalates in this subcategory, but the "melting points" are often pour points and the boiling points are measured at greatly reduced pressures. It can be safely extrapolated that the melting points of all of the phthalate esters in this subcategory are <0°C and the boiling points are all >300°C (>400°C for most substances).

Cousins and Mackay give best values for DnOP, DNP, DINP, DIDP, 610P, 711P, DUP, and DTDP for water solubility, vapor pressure, and partition coefficient. Data on 711P, which is a mixture of C7, C9, and C11 isomers, covers three CAS numbers in this subcategory (e.g., dinonyl, diundecyl, and nonyl undecyl). The physicochemical properties of these remaining phthalate esters may be adequately estimated by a combination of read-across and modeling.

Hydrolysis half lives and atmospheric photodegradation rates are calculated by EPI Suite™ (2000). Phthalate ester hydrolysis rates are quite low and not a significant fate route. Environmental distribution was modeled by the EQC model, Levels I and III. No additional measurements of the physicochemical or fate properties of this subcategory are necessary.

Mammalian Toxicity:

Acute Toxicity. The available data on phthalates spanning the carbon range from C8-C13 indicate that phthalate esters in the high molecular weight subcategory are not toxic by acute oral and dermal administration; LD50 values of all substances tested exceed the maximum amounts which can be administered to the animals. Some of these data have been published (e.g., Krauskopf, 1973; Lawrence *et al.*, 1975), but there is also a substantial body of unpublished data. There are fewer data available on inhalation toxicity; only DINP and DIDP have been tested. However, the phthalates in the high molecular weight subcategory have extremely low vapor pressures, and exposure by inhalation at potentially hazardous levels is not anticipated. Thus, further testing of the acute toxic properties of these materials is not warranted.

Repeated Dose Toxicity. Several substances ranging from C8-C11 have been tested for repeated dose toxicity in studies ranging from 21 days to two years (e.g., Barber *et al.*, 1987; Butala *et al.*, 1996; Lington *et al.*, 1997; David *et al.*, 2001). Ditridecyl phthalate (CAS # 119-06-2) has been studied by the Japan Ministry of Health and Welfare (unpublished report) and data for this substance is used as read-across data for DTDP. In addition results from repeat dose studies examining DINP (CAS # 68515-48-0) and DIDP (CAS # 68515-49-1) are used as read across for the di C9-C11 phthalates (CAS # 68515-43-5). The principal effects found are those associated with peroxisomal proliferation, including liver enlargement and induction of peroxisomal enzymes. As shown for example in a comparative study of liver effects (Barber *et al.*, 1987), the strongest inducers of peroxisomal proliferation were DEHP, DINP, and DIDP with substances of shorter and longer ester side chains (e.g., 610P, 711P, and DUP) showing less pronounced effects. Thus, it is reasonable to conclude that other members of this subcategory would show effects similar to but not more pronounced than those associated with DINP and DIDP. It should also be noted that the relevance of these findings to human health is, at best, questionable. It has been shown that these effects are mediated through the peroxisome proliferation-activated receptor alpha (PPARα; Valles *et al.*, 2000; Ward *et al.*, 1998), and that levels of PPARα are much higher in rodents than humans (Tugwood *et al.*, 1996; Palmer *et al.*, 1998). Thus, one would expect humans to be substantially less responsive than rodents to peroxisome proliferating agents. Empirical evidence supporting this postulation is provided by studies in primates in which repeated administration of DEHP and DINP (Hall *et al.*, 1999; Kurata *et al.*, 1998; Pugh *et al.*, 2000) had no effects on liver, kidney or testicular parameters.

In this regard it should also be noted that kidney enlargement is also commonly observed but normally without any pathological changes. As shown by Ward (1998), there is a component of the kidney changes which is also PPARα-related. It has also been shown that in male rats, DINP induces an alpha 2u-globulin nephropathy which is male rat-specific (Caldwell *et al.*, 1999: Schoonhoven *et al.*, 2001) but without relevance to humans (Baetcke *et al.*, 1992). Thus, as was true for the liver changes, the relevance of the kidney changes to human health is also questionable (Woodard, 1990).

Finally, some of the lower molecular weight phthalates can induce testicular atrophy when administered to juvenile rats at high levels. However, the higher molecular weight phthalates including DnOP, DINP, DIDP, 610P, and 711P do not induce testicular atrophy (Lington *et al.* 1993). Further, the testis was not a target organ for DINP in either marmosets (Hall *et al.*, 1999) or cynomolgus monkeys (Pugh *et al.*, 2000). Thus, testicular atrophy is not an effect associated with phthalates in the high molecular weight subcategory.

In summary, there is no need for further repeated dose studies of high molecular weight phthalates in rodents. The effects in rodents for this subcategory have been well described and are of questionable relevance to humans. Thus, further assessments of repeated dose toxicity of substances in this subcategory are unwarranted.

Genetic Toxicity (Salmonella). The majority of the substances in the subcategory of high molecular weight phthalates have been tested for genetic activity in the Salmonella assay, and all were inactive. One large program covering many of these substances was carried out by the National Institute of Environmental Health Sciences (Zeiger *et al.*, 1985). Similarly, a range of substances covering the majority of the carbon numbers in this subcategory were found to be inactive in mouse lymphoma tests (Barber *et al.*, 2000). Thus, no further testing of phthalates in the high molecular weight subcategory for the potential to induce point mutations is warranted.

Chromosomal Aberrations. Two representative members of the subcategory of high molecular weight phthalates (DINP and DIDP) have been tested for chromosomal mutation in the mouse micronucleus test (McKee *et al.*, 2000), and both were inactive. Ditridecyl phthalate (CAS # 119-06-2) induced neither structural chromosomal aberrations nor polyploidy in CHL cells up to the limit concentration of 4.75 mg/ml, in the absence or presence of an exogenous metabolic activation system (Japan Ministry of Health and Welfare, unpublished report). Further, all of the low molecular weight and transitional phthalates that have been tested were inactive. Thus, it is unlikely that the substances in this subcategory are chromosomal mutagens. No further testing for chromosomal aberrations is proposed for this subcategory.

Toxicity to reproduction. Reproductive toxicity tests in rats have been carried out with DINP (Waterman *et al.*, 1999), DIDP (Hushka *et al.*, 2000), a linear C7-C9 phthalate (CAS # 68515-41-3), a linear C9-C11 phthalate (Willoughby *et al.*, 2000), and ditridecyl phthalate (Japan Ministry of Health and Welfare, unpublished report). None of these affected fertility or profoundly affected male reproductive development. A slight decrease in offspring viability was reported for both DIDP and ditridecyl phthalate at levels associated with maternal effects. DnOP was tested for effects on fertility in a continuous breeding protocol in mice, and, like the other members of this subcategory, did not reduce fertility. Thus, it can be concluded that the subcategory of high molecular weight phthalates do not affect fertility and that no further reproductive testing of substances in this subcategory is warranted.

Developmental toxicity. Developmental toxicity tests in rats have been carried out with DINP; DIDP; C7-9 phthalate (CAS # 68515-41-3); C9-11 phthalate (CAS # 68515-43-5); and ditridecyl phthalate (CAS # 119-06-2) (Fulcher *et al.*, 2001; Waterman *et al.*, 1999; Japan Ministry of Health and Welfare, unpublished report). None of the substances tested affected litter size, fetal survival or bodyweight, and none produced teratogenic effects. Increased frequencies of developmental variants including dilated renal pelvis, and supernumerary lumbar and cervical ribs were found at levels associated with maternal effects. The toxicological significance of these developmental variants is unclear. DnOP was not teratogenic in mice when tested at very high levels. Thus, it can be concluded that this subcategory of high molecular weight phthalates do not produce profound developmental effects in rodents and no further testing of substances in this subcategory is warranted.

Environmental Toxicity:

Among the higher phthalates, acute aquatic test data in fish, invertebrates and algae are available for DINP, 610P, 711P, DUP, DIDP, and DTDP. None of these exhibit acute or chronic toxicity when tested at the maximum attainable water concentration (Staples *et al.*, 1997a). These phthalates all contain alkyl chain lengths in the range of C7 to C13, as do all the members of this subcategory. In fact, three of these (610P, DUP, and DTDP) are contained within this subcategory of CAS numbers. The remaining members of this subcategory are all various mixtures of C7 through C11 alkyl chain isomers. The fact that these phthalates do not show acute or chronic toxicity is due to their water solubility being well below an effect concentration (Parkerton and Konkel, 2000).

TEST PLAN SUMMARY

The American Chemistry Council, Phthalate Esters Panel, HPV Testing Group believes that there is a sufficient amount of information available on phthalate esters (as a chemical class) to substantially characterize the human health effects and environmental fate and effects endpoints for all members of this category under the U.S. HPV Challenge program. No additional testing is proposed for these materials.

Low Molecular Weight Phthalate Subcategory

- Physicochemical property and environmental fate data for all subcategory members were either calculated using appropriate QSAR models or measured.
- A complete mammalian and environmental SIDS data set is available for DMP and DEP, with the exception of adequate reproductive data on DMP. The lack of developmental effects observed with DMP, coupled with chronic toxicity studies showing no effects on reproductive organs and used as read-across data to DEP, fulfills the SIDS requirements for this endpoint.

Transitional Phthalate Subcategory

- Physicochemical property and environmental fate data for all subcategory members were either calculated using appropriate QSAR models or measured.
- Complete mammalian toxicity SIDS data sets are available under the OECD SIDS HPV program for BBP and DEHP (reference compounds; only the reproductive and developmental data from DEHP are used in this submission, although there are also data for BBP which show equivalent results). Acute toxicity, mutagenicity and developmental toxicity data are available for many of the remaining HPV chemicals in this subcategory. Data from the reference compounds are used as read-across data to estimate the toxicity of the remaining untested members.
- There is a full environmental toxicity data set for BBP (reference compound), DHP, DIOP, and 711P. BBP exhibits aquatic toxicity. However, there is an apparent cut-off for acute and chronic effects at dihexyl phthalate and higher; these results are further

confirmed with QSAR modeling. Based on data for subcategory members and read-across data from reference substances, acute or chronic aquatic effects are not expected for the remaining untested subcategory members.

High Molecular Weight Phthalate Subcategory

- Physicochemical property and environmental fate data for all subcategory members were either calculated using appropriate QSAR models or measured.
- Complete mammalian toxicity SIDS data sets are available for DINP, DIDP, and ditridecyl phthalate (reference compounds). Acute toxicity, repeated dose toxicity, mutagenicity and reproductive/developmental toxicity data are available for several of the remaining HPV chemicals in this subcategory. Studies from the reference compounds are used as read-across data to predict the toxicity of the remaining untested members.
- There is a full environmental toxicity data set for 610P, DINP (reference compound), DIDP (reference compound), DUP, and DTDP. Based on their poor water solubility, all reliable measured data for these chemicals show no effects to aquatic organisms from acute or chronic exposures. Based on data for subcategory members and read-across data from reference substances, acute and chronic aquatic effects are not expected for the remaining untested subcategory members.

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*The list of references is not a comprehensive bibliography of all of the phthalate ester literature, merely a series of papers which illustrate key points made in the text. The information in these papers also supplements the robust summaries developed for toxicology studies of listed substances in tests addressing specific SIDS endpoints.

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Appendix 1:
ACC, Phthalate Esters Panel, HPV Testing Group Literature Search

A. Review of Environmental Endpoints

The following documents were identified from the literature search as possible robust summary reviews for the ACC phthalates. Provided with each reference is the reason for its exclusion from the data review set.

1) Kleerebezem, R., *et al.*, Anaerobic Biodegradability of Phthalic Acid Isomers and Related Compounds, *Biodeg* 10 (1) 1999, p. 63-67.

> *Anaerobic study not a conventional test design or SIDS endpoint. HPV focusing on aerobic biodegradation endpoints.*

2) Gunatilleka, A., *et al.*, Models for Estimating the Non-specific Aquatic Toxicity of Organic Compounds. *Analytical Communications* 36 (6) 1999 p. 235-242.

> *New model for predicting aquatic toxicity endpoints. Laboratory data used in place of models. Phase III may identify models for use in filling data gaps versus testing.*

3) Zou, E. et al, Effects of Exposure to Diethyl Phthalate, 4-(tert)-octylphenol, and 2,4,5-trichlorobiphenyl on Activity of Chitobiase in the Epidermis and Hepatopancreas of the Fiddler Crab, *Uca pugilator*, COMPARATIVE BIOCHEMISTRY and PHYSIOLOGY 122 (1) 1999 p. 115-120.

> *Data generated not a SIDS endpoint.*

4) Kurane, R., Microbial Degradation and Treatment of Polycyclic Aromatic Hydrocarbons and Plasticizers, ANNALS of the NEW YORK ACADEMY of SCIENCE, Vol 829.

> *Abstract from book chapter and conference on bioremediation of surface and subsurface contamination. Methodology review.*

5) Mark, U., *et al.*, Analysis of the ECETOC Aquatic Toxicity (EAT) Database. V- The Relevance of *Daphnia magna* as a Representative Species. *Chemosphere* 36 (1) 1998.

> *A review of existing data through ECETOC, and a comparison of Daphnid sensitivity to other species. Not applicable to HPV robust summaries.*

6) Russom C., *et al.*, Predicting Modes of Toxic Action from Chemical Structure: Acute Toxicity in the Fathead Minnow (*Pimephales promelas*). *Environ Toxicol Chem* 16 (5) 1997.

> *Classification of chemicals in categories based upon their mode of toxicity. Not relevant to HPV robust summaries.*

7) Ejlertsson, J. *et al.*, Anaerobic Degradation of Phthalate Acid Esters During Digestion of Municipal Solid Waste Under Landfilling Conditions. *Biodeg* 7 (4) 1996.

> *Anaerobic degradation not a SIDS endpoint. Not a routine test design.*

8) Yan, H. *et al.*, Kinetics of Phthalate Ester Biodegradation by *Chlorella pyrenoidosa*. *Environ Toxicol Chem* **14** (6) 1995.

Biodegradation through plant bioaccumulation (modified algal study), not a SIDS endpoint.

9) Rhodes, J. *et al.*, Chronic Toxicity of 14 Phthalate Ester to *Daphnia magna* and Rainbow Trout (*Oncorhynchus myskiss*). *Environ Toxicol Chem* **14** (11) 1995.

Review article on chronic study endpoints for daphnids and fish. HPV robust summaries are focusing on acute endpoints only.

The following list contains literature search documents which are also referenced in comprehensive review paper (Staples *et al.*, 1997).

* Represent portions of the document reviewed for robust summaries.

1) Acute Toxicity of Fourteen Phthalate Esters to Daphnia magna, CMA report, Study performed by Springborn Bionomics 1984.

2) Acute Toxicity of Fourteen Phthalate Esters to Freshwater Algae, Selenastrum capricornutum, CMA report, Study performed by Springborn Bionomics 1984.

3) Acute Flow-Through Toxicity of Thirteen Phthalate Esters to Fathead Minnow Pimephales promelas, CMA report, Study performed by Springborn Bionomics 1984.

4) Acute Toxicity of Thirteen Phthalate Esters to Bluegill Sunfish L. macrochirus, CMA report, Study performed by Springborn Bionomics 1984.

5) Chronic Toxicity of Fourteen Phthalate Esters to Daphnia magna, CMA report, Study performed by Springborn Bionomics 1984.

6) Acute Toxicity of Thirteen Phthalate Esters to Sheepshead Minnow Cyprinodon variegatus, CMA report, Study performed by Springborn Bionomics 1984.

7) Acute Toxicity of Fourteen Phthalate Esters to Rainbow Trout Oncorhynchus mykiss, CMA report, Study performed by Springborn Bionomics 1984.

8) Acute Flow-through Toxicity of Fourteen Phthalate Esters to Rainbow Trout Oncorhynchus mykiss, CMA report, Study performed by Springborn Bionomics 1984.

9) Acute Toxicity of Twelve Phthalate Esters to Mysid Shrimp Mysidopsis bahia, CMA report, Study performed by Springborn Bionomics 1984.

10) Acute Toxicity of Twelve Phthalate Esters to Paratanytarsus parthenogenia, CMA report, Study performed by Springborn Bionomics 1984.

11) Shake Flask Biodegradation of Fourteen Commercial Phthalate Esters. CMA report, Study performed by Syracuse Research Corp. 1983.

12) Activated Sludge Biodegradation of Twelve Commercial Phthalate Esters. CMA report, Study performed by Syracuse Research Corp. 1983.

B. Review of Mammalian Toxicity Endpoints

The following documents were identified from the literature search as possible robust summary reviews for the ACC phthalates. Those studies marked by an asterisk (*) were not used for robust summaries as they either contained insufficient information to assess data quality or were not relevant SIDS endpoints. Provided with each marked reference is the reason for its exclusion from the data review set.

1. <u>131-11-3 1,2-benzenedicarboxylic acid, dimethyl ester</u>

Acute Toxicity

David, R. *et al.*, (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols. <u>In</u>: Patty's Toxicology, Fifth edition, Vol. 6, Bingham E., B. Cohrssen and C.H. Powell (eds.), John Wiley & Sons, Inc. pp. 635-932.

Draize, J. (1948). Toxicological investigations of compounds proposed for use as insect repellants, A. Local and system effects following topical skin application. Acute oral toxicity. C. Pathological Examination", Journal of Pharmacology and Experimental Therapeutics, 93, 26-39.

Genetic Toxicity - Mutagenicity

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356.* (May 1995).

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*D. Agarwal, W. Lawrence, L. Nunez and J. Autian (1985). Mutagenicity evaluation of phthalic acid esters and metabolites. *Journal of Toxicology and Environmental Health* **16**:61-69.

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*E. Barber, M. Cifone, J. Rundell, A. Lington, B. Astill, E. Moran, A. Mulholland, E. Robinson and B. Schneider (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* **20**:69-80.

*Seed, J. (1982). Mutagenic activity of phthalate esters in bacterial liquid suspension assays. *Environmental Health Perspectives* 45:111-114.

> **Although data are mixed, weight of evidence from above screening studies provide supportive information that material is non-mutagenic.*

Genetic Toxicity - Chromosomal Aberration

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356.* (May 1995).

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> **Weight of evidence from above screening studies provide supportive information that material is not genotoxic.*

Repeated Dose Toxicity

Draize, J. H. (1948). Toxicological investigations of compounds proposed for use as insect repellants, A. Local and system effects following topical skin application. Acute oral toxicity. C. Pathological Examination", Journal of Pharmacology and Experimental Therapeutics **93**:26-39.

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356.* (May 1995).

*A. Lehman (1955). Insect repellents. *Food and Drug Officials of the United States, Quarterly Bulletin* **19**:87-99.

*L. Timofievskaya, *et al.* (1974). Experimental research on the effect of phthalate plasticizers on the body. *Gigiena i Sanitariya*, **12**:26-28 (English translation of abstract.).

> **Above studies provide insufficient information to support data quality.*

Developmental Toxicity/Teratogenicity

Field, *et al.* (1993). Developmental toxicity evaluation of diethyl and dimethyl phthalate in rats. Teratology **48**:33-44.

A. Singh, W. Lawrence, and J. Autian. (1972). Teratogenicity of phthalate esters in rats. *Journal of Pharmaceutical Science* **61**:51-55.

*M. Plasterer, W. Bradshaw, G. Booth, M. Carter, R. Schuler, and B. Hardin (1985). Developmental toxicity of nine selected compounds following prenatal exposure in the mouse. *Journal of Toxicology and Environmental Health* **15**:25-38.

*B. D. Hardin, R. Schuler, J. Burg, G. Booth, K. Hazelden, K. MacKenzie, V. Piccirillo and K. Smith (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogenesis, Carcinogenesis and Mutagenesis* 7:29-48.

**Above are screening study only; less relevant for HPV robust summaries.*

Toxicity to Reproduction

*P. Foster, L. Thomas, M. Cook and S. Gangolli (1980). Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. *Toxicology and Applied Pharmacology* **54**:392-398.

*C. Harris, P. Henttu, M. Parker, and J. Sumpter (1997) The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* **105**:802-811.

*S. Oishi and H. Hiraga (1980). Effect of phthalic acid esters on mouse testis. *Toxicology Letters* **5**:413-416.

*B. Fredricsson, L. Möller A. Pousette, and R. Westerholm (1993). Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacology and Toxicology* **72**:128-133.

**Above studies examined specific testicular, androgenic, or estrogenic effects. Studies less relevant to HPV robust summaries.*

2. <u>84-66-2 1,2-benzenedicarboxylic acid, diethyl ester</u>

Acute Toxicity

Eastman Kodak Company, Rochester NY (1968). Diethyl phthalate. Acute dermal toxicity. Unpublished report.

Eastman Kodak Company, Rochester NY (1968). Diethyl phthalate. Acute inhalation toxicity. Unpublished report.

*David, R. *et al.*, (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols. <u>In</u>: Patty's Toxicology, Fifth edition, Vol. 6, Bingham E., B. Cohrssen and C.H. Powell (eds.), John Wiley & Sons, Inc. pp. 635-932.

Kodak unpublished study not available for review.

*D. Brown, K. Butterworth, I. Gaunt, P. Grassom, and S. Gangolli (1978). Short-term oral toxicity study of diethyl phthalate in the rat. *Food and Cosmetic Toxicology* **16**: 415-422.

Screening study; insufficient information to support data quality.

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans, and W. Speck (1985). Mutagenicity testing of d-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* 7:213-232.

*W. Kozumbo and R. Rubin (1982). Assessment of the mutagenicity of phthalate esters. *Environmental Health Perspectives* **45**:103-109

*D. Agarwal, W. Lawrence, L. Nunez, and J. Autian (1985). Mutagenicity evaluation of phthalic acid esters and metabolites. *Journal of Toxicology and Environmental Health* **16**:61-69.

*Seed, J. (1982). Mutagenic activity of phthalate esters in bacterial liquid suspension assays. Environmental health perspectives 45:111-114.

**Although data are mixed, weight of evidence from above screening studies provide supportive information that material is non-mutagenic.*

Genetic Toxicity - Chromosomal Aberration

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356.* (May 1995).

*M. Ishidate and S. Odashima (1977). Chromosome tests with 134 compounds on Chinese Hamster Cells in vitro - A screening for chemical carcinogens. *Mutation Research*, **48**:337-354.

*KTsuchiya and KHattori (1976). Chromosomal study on human leucocyte cultures treated with phthalic acid esters. *Hokkaidoritsu Eisei Kenkyusho Ho* **26**:114.

**Above screening studies provide supportive information that material is not genotoxic.*

Repeated Dose Toxicity

D. Brown, K. Butterworth, I. Gaunt, P. Grassom, and S. D. Gangolli (1978). Short-term oral toxicity study of diethyl phthalate in the rat. *Food and Cosmetic Toxicology,* **16**:415-422.

NTP (1995). Toxicology and carcinogenesis studies of diethylphthalate in F344/N rats and B6C3F1 mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss Cd-1 mice. *NTP TR 429, NIH Publication No. 95-3356.* (May 1995).

Developmental Toxicity/Teratogenicity

A. Singh, W. Lawrence, and J. Autian. (1972). Teratogenicity of phthalate esters in rats. *Journal of Pharmaceutical Science* **61**:51-55.

Field, *et al.* (1993). Developmental toxicity evaluation of diethyl and dimethyl phthalate in rats. *Teratology* **48**:33-44.

*B. Hardin, R. Schuler, J. Burg, G. Booth, K. Hazelden, K. MacKenzie, V. Piccirillo, and K. Smith (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogenesis, Carcinogenesis and Mutagenesis* **7**:29-48 .

Screening study only; less relevant for HPV robust summaries.

Toxicity to Reproduction

J. Lamb, IV, R. Chapin, C. Teague, A. Lawton, and J. Reel (1987). Reproductive effects of four phthalate acid esters in the mouse. *Toxicology and Applied Pharmacology* **88**:255-269.

*P. Foster, L. Thomas, M. Cook, and S. Gangolli (1980). Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. *Toxicology and Applied Pharmacology* **54**:392-398.

*C. Harris, P. Henttu, M. Parker, and J. Sumpter (1997). The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* **105**:802-811.

*B. Fredricsson, L. Möller, A. Pousette, and R. Westerholm (1993). Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacology and Toxicology* **72**:128-133.

*H. Jones, D. Garside, R. Liu, and J. Roberts (1993). The influences of phthalate esters on leydig cell structure and function in vitro and in vivo. *Environmental and Molecular Pathology* **58**:179-193.

> **Above studies examined specific testicular, androgenic, or estrogenic effects. Studies less relevant to HPV robust summaries.*

*BASF AG, unpublished data (1974).

> *Unpublished study not available for review.*

3. **<u>68515-50-4 1,2,-benzenedicarboxylic acid, dihexyl ester, branched and linear</u>**

Genetic Toxicity - Chromosomal Aberration

ExxonMobil Biomedical Sciences, Inc. (1994). In Vivo Mammalian Bone Marrow Micronucleus Assay. Unpublished study. Company unpublished studies.

Repeated Dose Toxicity

Esso Research and Engineering Company (1962). Dihexyl Phthalate: 90-Day dietary administration study in rats and dogs. Unpublished study.

4. **<u>68515-44-6 1,2-benzenedicarboxylic acid, diheptyl ester, branched and linear</u>**

> *No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).*

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* **20**:69-80.

Developmental Toxicity/Teratogenicity

J. Hellwig, H. Freudenberger, and R. Jackh (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.

> *Developmental toxicity thought to be due to C4 to C6 constituents in 711P mixture. Di-heptyl phthalate contains >10% C4 to C6 molecules; thus 711P data are conservatively used to evaluate this substance.*

5. **71888-89-6 1,2-benzenedicarboxylic acid, di C6-8 branched alkyl ester, C7 rich**

Acute Toxicity

MB Research Laboratories (1979). Test for oral toxicity in rats. Project No. MB 79-3967. Conducted for Exxon Biomedical Sciences, Inc. Unpublished report.

MB Research Laboratories (1979). Test for dermal toxicity in rats. Project No. MB 79-3967. Conducted for Exxon Biomedical Sciences, Inc. Unpublished report.

Genetic Toxicity - Mutagenicity

Exxon Biomedical Sciences, Inc. (1995). Microbial Mutagenesis in Salmonella Mammalian Microsome Plate Incorporation Assay. Project No. 167634. Unpublished report.

Genetic Toxicity - Chromosomal Aberration

Hazleton Laboratories America, Inc. (1991). Mutagenicity Test in an In Vitro Cytogenetic Assay. Project No. 181232. Conducted for Exxon Biomedical Sciences, Inc., unpublished report.

Repeated Dose Toxicity

No studies found.

Developmental Toxicity/Teratogenicity

Exxon Biomedical Sciences, Inc. (1997). Developmental toxicity study in rats with diisoheptyl phthalate. Unpublished report.

Toxicity to Reproduction

No studies found.

6. **27554-26-3 1,2,-benzenedicarboxylic acid, diisooctyl ester**

Acute Toxicity

*Krauskoph, L. (1973). Studies on the toxicity of phthalates via ingestion. *Environmental Health Perspectives.* **3**:61-72.

> *Secondary reference; insufficient to assess data quality.*

Genetic Toxicity - Mutagenicity

Goodyear Fiber and Polymer Products Research Division (1981). Laboratory Report No. 81-4-7. Mutagenicity evaluation of di-isooctyl phthalate (USS Chemical). EPA document number 878210369, Fiche no. OTS0206046.

Litton Bionetics Inc. (1981). Evaluation of di-isooctyl phthalate in the in vitro transformation of BALB/c3T3 cells assay. Final Report. EPA Document No. 878101226 Fiche No. OTS 0206260.

Genetic Toxicity - Chromosomal Aberration

No studies found.

Repeated Dose Toxicity

*S. Shibko and H. Blumenthal (1973). Toxicology of phthalic acid esters used in food-packaging materials. *Environmental Health Perspectives* **3**:131-137.

Abbreviated non-GLP study; insufficient to support data quality.

Developmental Toxicity/Teratogenicity

No studies found.

Toxicity to Reproduction

No studies found.

7. **<u>117-84-0 1,2,-benzenedicarboxylic acid, dioctyl ester</u>**

Acute Toxicity

R. Dogra, S. Khanna, L. Shukla, S. Srivastava, M. Bhatnagar, P. Gupta, and R. Shanker (1987). Modification of immune response in rats by di-octyl phthalate. *Ind. Health* **25**:97-101.

R. Dogra, K. Chandra, S. Chandra, S. Khanna, S. N. Srivastava, L. Shukla, J. C. Katiyar, and R. Shanker (1989). Di-octyl phthalate induced altered host resistance: viral and protozoal models in mice. *Ind. Health* **27**:83-87.

* David, R. *et al.*, (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols. <u>In</u>: Patty's Toxicology, Fifth edition, Vol. 6, Bingham E., B. Cohrssen and C.H. Powell (eds.), John Wiley & Sons, Inc. pp. 635-932.

Secondary reference citing older study.

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans and W. Speck. (1985). Mutagenicity testing of d-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* **7**:213-232.

*Seed, J. (1982). Mutagenic activity of phthalate esters in bacterial liquid suspension assays. Environmental health perspectives **45**:111-114.

Limited screening study in one tester strain.

Genetic Toxicity - Chromosomal Aberration

No studies found.

Repeated Dose Toxicity

R. Poon, P. Lecavalier, R. Mueller, V. E. Valli, B. G. Procter, and I. Chu (1997). Subchronic oral toxicity of di-n-octyl phthalate and di(2-ethylhexyl) phthalate in the rat. *Food and Chemical Toxicology* **35**:225-239.

*B. Lake, W. Rijcken, T. Gray, J. Foster, and S. Gangolli (1984). Comparative studies of the hepatic effects of di- and mono-n-octyl phthalates, di-(2-ethylhexyl) phthalate and clofibrate in the rat. *Acta. Pharmacol. et Toxicol.* **54**:167-176.

*B. Lake, T. Gray, and S. Gangolli (1986). Hepatic effects of phthalate esters and related compounds- in vivo and in vitro correlations. *Environmental Health Perspectives*. **67**:283-290.

**Above studies examined specific effects on the liver. Studies less relevant to HPV robust summaries.*

Developmental Toxicity/Teratogenicity

B. Hardin, R. Schuler, J. Burg, G. Booth, K. Hazelden, K. MacKenzie, V. Piccirillo, and K. Smith (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogenesis, Carcinogenesis and Mutagenesis* **7**:29-48.

*A. Singh, W. Lawrence, and J. Autian (1972). Teratogenicity of phthalate esters in rats. *Journal of Pharmaceutical Science* **61**:51-55.

Abbreviated non-GLP study; insufficient to support data quality.

*T. Zacharewski, J. Clemons, M. Meek, Z. Wu, M. Fielden, and J. Matthews (1998). Examination of the in vitro and in vivo estrogenic activities of eight commercial phthalate esters. *Toxicological Sciences* **42**:282-293.

Study examined estrogenic effects; less relevant to HPV robust summaries.

Toxicity to Reproduction

J. Heindel, D. Gulati, R. Mounce, S. Russell, and J. Lamb (1989). Reproductive toxicity of three phthalic acid esters in a continuous breeding protocol. *Fundamental and Applied Toxicology* **12**:508-518.

*S. Oishi and K. Hiraga (1980). Testicular atrophy induced by phthalate acid esters: Effect on testosterone and zinc concentration. *Toxicology and Applied Pharmacology*, **53**:35-41.

*P. Foster, L. Thomas, M. Cook, and S. Gangolli (1980). Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. *Toxicology and Applied Pharmacology*. **54**:392-398.

*C. Harris, P. Henttu, M. Parker, and J. Sumpter (1997). The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* **105**:802-811.

**Above studies examined specific testicular, androgenic, or estrogenic effects. Studies less relevant to HPV robust summaries.*

8. **<u>68515-40-2 1,2-benzenedicarboxylic acid, benzyl C7-9 branched and linear alkyl esters</u>**

Data from Monsanto Company unpublished reports.

9. 111381-89-6 1,2-benzenedicarboxylic acid (C7, C9) ester, branched and linear

The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* **20**:69-80.

Developmental Toxicity/Teratogenicity

J. Hellwig, H. Freudenberger, and R. Jackh. (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.

Developmental toxicity thought to be due to C4 to C6 constituents in 711P mixture. Di-(C7, C9) phthalate contains >10% C4 to C6 molecules; thus 711P data are conservatively used to evaluate this substance.

10. 68648-93-1 1,2-benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters

No relevant studies found.

11. 68515-45-7 1,2,-benzenedicarboxylic acid, dinonyl ester, branched and linear

No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* **20**:69-80.

Developmental Toxicity/Teratogenicity

*J. Hellwig, H. Freudenberger, and R. Jackh (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.

Developmental toxicity thought to be due to C4 to C6 constituents in 711P mixture. Di-nonyl phthalate contains <10% C4 to C6 molecules; thus 711P data are not relevant to this substance.

12. 68515-43-5 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters

Toxicity to Reproduction

Willoughby, C., Fulcher, S., Creasy, D., Heath, J., Priston, R., and Moore, N. (2000). Two generation reproduction toxicity studies of di-(C7-C9 alkyl) phthalate and di-(C9-C11 alkyl) phthalate in the rat. Reproductive Toxicology **14**:427-450.

Developmental Toxicity/Teratogenicity

Fulcher, S. *et al.* (2001). Developmental toxicity of di(C7-C9 alkyl) phthalate and di(C9-C11 alkyl)phthalate in the rat. Reproductive Toxicology **15**:95-102.

13. <u>84-77-5 1,2-benzenedicarboxylic acid, didecyl ester</u>

No relevant studies found.

14. <u>3648-20-2 1,2-benzenedicarboxylic acid, diundecyl ester</u>

Acute Toxicity

W. Lawrence, M. Malik, J. Turner, A. Singh, and J. Autian (1975). A toxicological investigation of some acute, short-term, and chronic effects of administering di-2-ethylhexyl phthalate (DEHP) and other phthalate esters. *Environmental Research* **9**:1-11.

*European Commission, European Chemicals Bureau, International Uniform Chemical Information Database (IUCLID). (1994). Diundecyl Phthalate Data Sheet. *Section 5.1, Version 3.0.4.*

> *Monsanto unpublished study not available for review.*

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans, and W. Speck (1985). Mutagenicity testing of di-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* **7**:213-232.

E. Barber, M. Cifone, J. Rundell, A. Lington, B. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* **20**:69-80.

Genetic Toxicity - Chromosomal Aberration

No studies found.

Repeated Dose Toxicity

BIBRA, The British Industrial Biological Research Association. A 21-day feeding study of di-undecyl phthalate to rats: effects on the liver and liver lipids. *EPA Document No. 40/85262007, Fiche No. OTS0509538.*

Developmental Toxicity/Teratogenicity

*J. Hellwig, H. Freudenberger, and R. Jackh (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.

> *Developmental toxicity thought to be due to C4 to C6 constituents in 711P mixture. Di(C11) phthalate contains <10% C4 to C6 molecules; thus 711P data are not relevant to this substance.*

Toxicity to Reproduction

*C. Harris, P. Henttu, M. Parker and J. Sumpter (1997). The estrogenic activity of phthalate esters in vitro. *Environmental Health Perspectives* **105**:802-811.

> *Study examined estrogenic effects; less relevant to HPV robust summaries.*

15. <u>85507-79-5 1,2-benzenedicarboxylic acid, di (C11) ester, branched and linear</u>

No relevant studies found.

16. **<u>111381-90-9 1,2-benzenedicarboxylic acid, (C7, C11) ester, branched and linear</u>**

No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* **20**:69-80.

Developmental Toxicity/Teratogenicity

J. Hellwig, H. Freudenberger, and R. Jackh (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.

Developmental toxicity thought to be due to C4 to C6 constituents in 711P mixture. Di-(C7, C11) phthalate contains >10% C4 to C6 molecules; thus 711P data are conservatively used to evaluate this substance.

17. **<u>111381-91-0 1,2-benzenedicarboxylic acid (C9, C11) ester, branched and linear</u>**

No studies found on this CAS number, per se. The following data are on di (heptyl, nonyl, undecyl) phthalate (di-711-phthalate).

Genetic Toxicity - Mutagenicity

E. Barber, M. Cifone, J. Rundell, R. Przygoda, B. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider (1999). Results in the L5178Y mouse lymphoma and the in vitro transformation of Balb 3T3 cell assays for eight phthalate esters. *Journal of Applied Toxicology* 20:69-80.

Developmental Toxicity/Teratogenicity

*J. Hellwig, H. Freudenberger, and R. Jackh (1997). Differential prenatal toxicity of branched phthalate esters in rats. *Food and Chemical Toxicology* **35**:501-512.

Developmental toxicity thought to be due to C4 to C6 constituents in 711P mixture. Di(C9, C11) phthalate contains <10% C4 to C6 molecules; thus 711P data are not relevant to this substance.

18. **<u>68515-47-9 1,2,-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich</u>**

Acute Toxicity

Bio/dynamics, Inc. (1981). Acute Oral Toxicity in Rats. Conducted for Exxon Biomedical Sciences, Inc. Unpublished Report.

Bio/dynamics, Inc. (1981). Acute Dermal Toxicity in Rabbits. Conducted for Exxon Biomedical Sciences, Inc. Unpublished Report.

*Krauskoph, L. (1973). Studies on the toxicity of phthalates via ingestion. *Environmental Health Perspectives.* **3**:61-72.

Secondary reference; insufficient to assess data quality.

Genetic Toxicity - Mutagenicity

E. Zeiger, S. Haworth, K. Mortelmans, and W. Speck (1985). Mutagenicity testing of d-(2-ethylhexyl)phthalate and related chemicals in Salmonella. *Environmental Mutagenesis* **7**:213-232.

Table 3
Toxicology Data Summary
Phthalate Esters

Alkyl Backbone Carbon Length	CAS Number	Chemical Name	Acute Oral LD50	Acute Dermal LD50	Acute Inhalation LC50	Repeated Dose Toxicity	Genetic Toxicity (Ames)	Genetic Toxicity (Chrom. Ab.)	Reproductive Toxicity	Developmental Toxicity/Teratogenicity	Acute Fish 96hr LC50 (A) mg/L	Acute Daphnia 48hr EC50 (B) mg/L	Algal Tox 96 hr EC50 (C) mg/L	Chronic Fish (D) mg/L (NOEC)
Low Molecular Weight Phthalate Esters														
C1	131-11-3	dimethyl ester **(DMP)**	6.9 g/kg (rat)	>10 ml/kg (rabbit) (4)	>4 mg/l (rat) (ra DEP)	LOAEL = 4 ml/kg, kidney,liver effects (90 day dermal study, rabbits)	Negative	Negative (CHO)	NOAEL = 3250 mg/kg/day (mice) (ra DEP)	NOAEL rat (maternal) 840mg/kg/day NOAEL (develop) >3570 mg/kg/day	56	46	142	11 (LOEC = 24) (60 days)
C2	84-66-2	diethyl ester **(DEP)**	>5.0 g/kg (rat) (4)	>20 ml/kg (guinea pig)	>4.64 mg/l (rat, nominal)	NOAEL (rat, dietary, 16 weeks) males ~750 mg/kg/day; females ~150 mg/kg/day	Negative	Negative (CHO)	NOAEL (mice) F0, F1, F2 = 3250 mg/kg/day	NOAEL rat (maternal) 200 mg/kg/day NOAEL (develop) 1910 mg/kg/day	12	86	16	t (ra DMP)
Transitional Phthalate Esters														
C4, C7	85-68-7	butylbenzyl ester **(BBP)**	2330 mg/kg	>10,000 mg/kg (rabbit)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 151 mg/kg/day	Negative (Ames, mouse lymphoma)	Negative or equivocal (CHO in vitro, micronucleus in vivo)	One gen. NOAEL (rat) >418 mg/kg/day	NOAEL (rat) = 418 mg/kg/day (mouse) = 182 mg/kg/day	0.82	nt >0.96 (9)	0.21	nt 0.20 (12) (109 days)
C6	68515-50-4	dihexyl ester branched & linear **(DHP)**	29.6 ml/kg (rat) (ra DnHP)	>10 - 25 g/kg (rabbit) (ra BBP, DEHP)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 380 mg/kg/day NOAEL (dog) = 180 mg/kg/day	Negative (ra DnHP)	Negative (micronucleus, in vivo)	Two gen. LOAEL (mice) = 430 mg/kg/day (ra DnHP)	NOAEL (rat) = 357 - 418 mg/kg/day (ra DEHP, BBP)	nt >0.2 (9)	nt >0.18 (9)	nt >0.33 (9)	nt 0.22 (12) (111 days)
C6	84-75-3	di-n-hexyl ester **(DnHP)**	29.6 ml/kg (male) 38.9 ml/kg (female) (rat)	>10 - 25 g/kg (rabbit) (ra BBP, DEHP)	10,620 mg/m3 (rat) (ra DEHP)	LOAEL (rat) = 1800 mg/kg/day liver effects (21 day, diet)	Negative (Ames)	Negative (ra DHP)	Two gen. LOAEL (mice) = 430 mg/kg/day	LOAEL (mice) = 9900 mg/kg	nt (ra DHP)	nt (ra DHP)	nt (ra DHP)	nt (ra DHP)
C6-8	71888-89-6	di C6-8 branched **(DIHP)**	>10g/kg (rat)	>3.16 g/kg (rabbit)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 50 - 151 mg/m3 (ra DEHP, BBP)	Negative	Negative (CHO in vitro)	NOAEL = 60 - 418 mg/kg/day (ra DEHP, BBP)	NOAEL rat (maternal) 750 mg/kg/day NOAEL (devel) 300 mg/kg/day	nt >0.20 (9)	nt (ra DHP)	nt (ra DHP)	nt 1 mg/kg feed (11, 12) (270 days)
C8	117-81-7	diethylhexyl ester **(DEHP)**	9800 mg/kg bw (mouse)	25,000 mg/kg bw (rabbit)	10,620 mg/m3 (rat)	NOAEL (rat) = 50 mg/m3	Negative	Negative (CHO in vitro)	60 days, male rat NOAEL = 69 mg/kg bw/day	NOAEL (rat, diet) = 357 mg/kg bw/day (maternal & develop)	nt >0.33 (9)	nt >0.32 (9)	nt >0.10 (9)	nt 0.32 (12) (35 days)
C7	68515-44-6	diheptyl ester branched & linear **(DInHP)**	>10g/kg (rat) (ra DIHP)	>3 g/kg (rabbit) (ra DIHP)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 50 - 151 mg/m3 (ra DEHP, BBP)	Negative (mouse lymphoma) (5)	Negative (ra DEHP)	NOAEL = 60 - 418 mg/kg/day (ra DEHP, BBP)	NOAEL (rat, oral) 200 mg/kg/day (maternal & develop) (5)	nt (ra DHP)	nt (ra DHP)	nt (ra DHP)	nt (ra DHP)
C8	27554-26-3	diisooctyl ester **(DIOP)**	>22.6 g/kg (rat) (4)	>3 g/kg (rabbit) (ra DIHP)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 50 - 151 mg/m3 (ra DEHP, BBP)	Negative	Negative (ra DEHP)	NOAEL = 60 - 418 mg/kg/day (ra DEHP, BBP)	NOAEL (rat, devel) = 200 - 300 mg/kg/day (ra DinHP, DIHP)	nt >0.23 (9)	nt >0.22 (9)	nt >1.30 (9)	nt (ra DHP)
C7, C9	111381-89-6	C7, C9, branched & linear **(Din79P)**	>22.6 g/kg (rat) (ra DIOP)	>3 g/kg (rabbit) (ra DIHP)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 50 - 151 mg/m3 (ra DEHP, BBP)	Negative (mouse lymphoma) (5)	Negative (ra DEHP)	NOAEL = 60 - 418 mg/kg/day (ra DEHP, BBP)	NOAEL (rat, oral) 200 mg/kg/day (maternal & develop) (5)	nt (ra DIOP)	nt (ra DIOP)	nt (ra DIOP)	nt (ra DHP)
C7, C11	111381-90-9	C7, C11, branched & linear **(711P)**	>22.6 g/kg (rat) (ra DIOP)	>3 g/kg (rabbit) (ra DIHP)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 50 - 151 mg/m3 (ra DEHP, BBP)	Negative (mouse lymphoma) (5)	Negative (ra DEHP)	NOAEL = 60 - 418 mg/kg/day (ra DEHP, BBP)	NOAEL (rat, oral) 200 mg/kg/day (maternal & develop) (5)	nt >0.21 (9)	nt >0.04 (9)	nt >1.60 (9)	nt 0.41 (12) (120 days)
C7, C12	16883-83-3	benzyl C8-oxybutyl **(B84P)**	>22.6 g/kg (rat) (ra DIOP)	>3 g/kg (rabbit) (ra DIHP)	10,620 mg/m3 (rat) (ra DEHP)	NOAEL (rat) = 50 - 151 mg/m3 (ra DEHP, BBP)	Negative (mouse lymphoma) (ra 711P)	Negative (ra DEHP)	NOAEL = 60 - 418 mg/kg/day (ra DEHP, BBP)	NOAEL (rat, maternal & devel) = 200 mg/kg/day (ra 711P)	nt >1000 (9)	nt (ra)	nt >1000 (9)	nt (ra 711P)
High Molecular Weight Phthalate Esters														
C6, C8, C10	68648-93-1	mixed decyl & hexyl and octyl esters **(610P)**	54 g/kg (rat) (ra DnOP)	>7.94 g/kg (rabbit) (ra B79P)	>4.4 mg/l (rat) (ra DINP)	NOAEL (rat) = 38 - 100 mg/kg/day (ra DnOP, in79P)	Negative (ra DnOP)	Negative (ra DINP)	NOAEL (mice, dietary) 7500 mg/kg/day (F1/F2) (ra DnOP)	NOAEL (rat, oral) = 500 mg/kg/day (ra in79P)	nt >0.24 (9)	nt >0.33 (9)	nt >0.10 (9)	nt (ra DHP)

Table 3
Toxicology Data Summary
Phthalate Esters

C8	117-84-0	dioctyl ester **(DnOP)**	13 g/kg (mice); 54 g/kg (rat)	>7.94 g/kg (rabbit) (ra B79P)	>4.4 mg/l (rat) (ra DINP)	NOAEL (rat, dietary, 13 week) 38.8 mg/kg/day	Negative	Negative (ra DINP)	NOAEL (mice, dietary) 7500 mg/kg/day (F1/F2)	NOAEL (mice, oral) = 9780 mg/kg/day (maternal & devel)	nt (ra)	nt (ra)	nt (ra)	nt (ra DHP)
C7, C7-9	68515-40-2	benzyl C7-C9 branched & linear **(B79P)**	>15.8 g/kg (rat)	>7.94 g/kg (rabbit)	>4.4 mg/l (rat) (ra DINP)	NOAEL (rat) = 38-100 mg/kg/day (ra DnOP, in79P)	Negative	Negative (ra DINP)	Two gen. NOAEL (rat) = 1% diet (repro effects); 0.5% (general toxicity) (ra in79P)	NOAEL (rat, oral) = 500 mg/kg/day (ra in79P)	nt >1000 (9)	nt (ra)	nt (ra)	nt (ra DHP)
C7-9	68515-41-3	(C7-C9) branched & linear alkyl ester **(in79P)**	>22 g/kg (rat)	>7.94 g/kg (rabbit) (ra B79P)	>4.4 mg/l (rat) (ra DINP)	NOAEL (rat) = 100 mg/kg	Negative	Negative (ra DINP)	Two gen. NOAEL (rat) = 1% diet (repro effects); 0.5% (general toxicity)	NOAEL(rat, oral) = 500 mg/kg/day	nt >1000 (9)	nt >0.8 (9)	nt (ra)	nt (ra DHP)
C8-10	28553-12-0 68515-48-0	diisononyl ester **(DINP)**	>10,000 mg/kg/day (rat)	>3.16 g/kg/day (rabbit)	>4.4 mg/l (rat)	NOAEL (rat) = 88 mg/kg/day	Negative (Ames, mouse lymphoma)	Negative (CHO in vitro, micronucleus in vivo)	NOAEL(rat) = 633 mg/kg/day	NOAEL(rat, oral) = 500 mg/kg/day	nt >0.16 (9)	nt >0.06 (9)	nt >1.80 (9)	nt 20 mg/kg feed (12, 13) (284 days)
C9	68515-45-7	dinonyl ester branched & linear **(DNP)**	>10 - >29 g/kg (rat) (ra DINP, DIDP)	>3.16 g/kg (rabbit) (ra DINP, DIDP)	>4 - >12 mg/l (rat) (ra DINP, DIDP)	NOAEL (rat) = 60-88 mg/kg/day (ra DIDP, DINP)	Negative (mouse lymphoma) (5)	Negative (ra DINP, DIDP)	NOAEL (rat = 633 mg/kg/day (ra DINP, DIDP)	NOAEL (rat, oral) = 500 mg/kg/day (ra DINP, DIDP)	nt (ra)	nt (ra)	nt (ra)	nt (ra DINP)
C9-11	68515-43-5	di-C9-C11 branched & linear **(911P)**	>10 - >29 g/kg (rat) (ra DINP, DIDP)	>3.16 g/kg (rabbit) (ra DIDP)	>4 - >12 mg/l (rat) (ra DINP, DIDP)	NOAEL (rat) = 60-88 mg/kg/day (ra DIDP, DINP)	Negative (ra DIDP)	Negative (ra DINP, DIDP)	NOAEL (rat = 633 mg/kg/day (ra DINP, DIDP)	NOAEL (rat, oral) = 500 mg/kg/day (ra DINP, DIDP)	nt (ra)	nt (ra)	nt (ra)	nt (ra DINP)
C10	84-77-5	didecyl ester **(DDP)**	>10 - >29 g/kg (rat) (ra DINP, DIDP)	>3.16 g/kg (rabbit) (ra DIDP)	>4 - >12 mg/l (rat) (ra DINP, DIDP)	NOAEL (rat) = 60-88 mg/kg/day (ra DINP, DIDP)	Negative (ra DIDP)	Negative (ra DINP, DIDP)	NOAEL (rat = 633 mg/kg/day (ra DINP, DIDP)	NOAEL (rat, oral) = 500 mg/kg/day (ra DINP, DIDP)	nt (ra)	nt (ra)	nt (ra)	nt (ra DINP)
C9-11	26761-40-0 68515-49-1	diisodecyl ester **(DIDP)**	>29,100 mg/kg/day (rat)	>3.16 g/kg/day (rabbit)	>12.5 mg/l (rat)	NOAEL (rat) = ~ 60 mg/kg/day	Negative (Ames, mouse lymphoma)	Negative (micronucleus in vivo)	NOAEL(rat) = 50 mg/kg/day	NOAEL(rat, oral) = 500 mg/kg/day	nt >0.62 (9)	nt >0.02 (9)	nt >0.80 (9)	nt 20 mg/kg feed (12, 13) (284 days)
C11	3648-20-2	diundecyl ester **(DUP)**	> 15 g/kg (rat) (4)	>7.9 g/kg (rabbit) (4)	>12.5 mg/l (rat) (ra DIDP)	NOAEL = ~ 282 mg/kg (dietary, rats, 3 week)	Negative (Ames & mouse lymphoma)	Negative (ra DIDP)	NOAEL (rat) = 50 mg/kg/day (ra DIDP)	NOAEL (rat, oral) = 250 - 500 mg/kg/day (ra DTP, DIDP)	nt >1.40 (9)	nt >0.02 (9)	nt >2.10 (9)	nt (ra DIDP)
C11	85507-79-5	di (C11) ester branched & linear **(DIUP)**	>10 - > 15 g/kg (rat) (ra DTDP, DUP)	>3 - >7 g/kg (rabbit) (ra DTDP, DUP)	>12.5 mg/l (rat)(ra DIDP)	NOAEL = ~ 282 mg/kg (dietary, rats, 3 week) (ra DUP)	Negative (ra DUP)	Negative (ra DIDP)	NOAEL (rat) = 50 mg/kg/day (ra DIDP)	NOAEL (rat, oral) = 250 - 500 mg/kg/day (ra DTP, DIDP)	nt (ra)	nt (ra)	nt (ra)	nt (ra DIDP)
C9, C11	111381-91-0	C9, C11, branched & linear **(Din911P)**	>10 - > 15 g/kg (rat) (ra DTDP, DUP)	>3 - >7 g/kg (rabbit) (ra DIDP, DUP)	>12.5 mg/l (rat)(ra DIDP)	NOAEL = ~ 282 mg/kg (dietary, rats, 3 week) (ra DUP)	Negative (mouse lymphoma) (5)	Negative (ra DIDP)	NOAEL (rat) = 50 mg/kg/day (ra DIDP)	NOAEL (rat, oral) = 250 - 500 mg/kg/day (ra DTP, DIDP)	nt (ra)	nt (ra)	nt (ra)	nt (ra DIDP)
C11-14	68515-47-9	di-C11-C14, C13 rich ester **(DTDP)**	>10 g/kg (rat)	>3.16 g/kg (rabbit)	>12.5 mg/l (rat)(ra DIDP)	NOAEL = ~ 282 mg/kg (dietary, rats, 3 week) (ra DUP)	Negative	Negative (ra DIDP, DTP)	NOAEL (rat) = 50 - 250 mg/kg/day (ra DIDP, DTP)	NOAEL (rat, oral) = 250 - 500 mg/kg/day (ra DTP, DIDP)	nt >0.15 (9)	nt >0.05 (9)	nt >0.60 (9)	nt (ra DIDP)
C13	119-06-2	ditridecyl **(DTP)**	>2 g/kg (rat)	>3.16 g/kg (rabbit) (ra DTDP)	>12.5 mg/l (rat) (ra DIDP)	NOAEL (rat) = 10 mg/kg/day; LOAEL = 50 mg/kg/day (F)	Negative	Negative (CHL cells)	NOAEL (rat) = 250 mg/kg/day (male); = 50 mg/kg/day (female)	NOAEL(rat, oral) = 250 mg/kg/day	nt (ra)	nt (ra)	nt (ra)	nt (ra DIDP)

Table 3
Toxicology Data Summary
Phthalate Esters

Highlighted substances are not in the High Production Volume Chemical Program but have data that are included to support the hazard evaluation of the phthalate ester category.

Footnotes:
(A) Rainbow Trout data presented. Data on other fish species availbale - Fathead minnow, Sheepshead minnow and Bluegill Sunfish, ect.
(B) *Daphnia magna* data presented. Data on other invertebrates available - Mysid shrimp, Midge, Brine shrimp, ect.
(C) *Selenastrum capricornutum* data presented. Data on other species availbale - *S.subspicatus, S. Costatum,* etc.
(D) Rainbow Trout data presented
ra read-across data from tested category members
t toxic
nt not toxic at saturation
nd no data
ex1 extent of biodegradation expected to be >60% in a 28-day OECD 301F ready biodegradation test procedure
ex2 extent of biodegradation expected to be >20% to 60% in a 28-day OECD 301F ready biodegradation test procedure
ex3 extent of biodegradation expected to be >10% to 20% in a 28-day OECD 301F ready biodegradation test procedure and capable of >60% in 56 days
Reference: Staples, C.A. et al, Aquatic Toxicity of Eighteen Phtthlates Ester, 1997, Environmental Toxicology and Chemistry Vol. 16, No. 5
(c #) Based upon algal cell number
(1) Biodegradation by Manometric Respirometer Method (OECD 301F) - unadapted inoculum
(2) Biodegration by Modified Sturm Method (OECD 301B) - unadapted inoculum
(3) Biodegradation by Shake Flask Method - adapted inoculum
(3.1) Biodegradation by Modified MITI Test (OECD 301C)
(4) Values reported in secondary reference (Patty's); robust summary not prepared due to insufficient information
(5) Test material (di heptyl, nonyl, undecyl phthalate) considered by EPA to be applicable to the following CAS nos: 111381-89-6, 111381-90-9, 111381-91-0, 68515-44-6, 68515-45-7, 3648-20-2
(6) Solvent used to enhance material solubility (acetone)
(7) Solvent used to enhance material solubility (DMF)
(8) 72 hr. *Scenedesmus subspicatus* data
(9) No statistically significant mortality in fish, or immobility in daphnia, or effect on algal growth in treatment solution saturated with test substance
(10) Fish tested: Fathead Minnow
(11) Feeding study; dose was 1 mg/Kg fish feed
(12) No statistically significant effects in either treatment solutions saturated with test substance or in feeding study
(13) Feeding study (2-generation); dose was 20 mg/Kg fish feed

Table 3
Toxicology Data Summary
Phthalate Esters

Chronic Daphnia 21 da (B) mg/L (NOEC)	Percent Biodegradation (28 da)
9.6 (LOEC = 23) (MATC = 14.9)	>99 primary 85.9 ultimate (3) Rapidly Biodegradable
25 (LOEC = 59) (MATC = 38.4)	>99 primary 94.6 ultimate (3) Rapidly Biodegradable
0.28 (LOEC = 1.4) (MATC = 0.63)	81 (14 days) (3.1) >99 primary 96 ultimate (3) Rapidly Biodegradable
nd	79.7 (1) Rapidly Biodegradable
nd	Rapidly Biodegradable (ra, ex1)
nt 0.92 (12)	82.2 (1) Rapidly Biodegradable
nt 0.16 (12)	Rapidly Biodegradable (ra, ex1)
nt (ra DIHP)	Rapidly Biodegradable (ra, ex)
nt (ra DIHP)	>99 primary 57 ultimate (3) Rapidly Biodegradable
nt (ra DIHP)	Rapidly Biodegradable (ra, ex1)
nt (ra DIHP)	Rapidly Biodegradable (ra, ex1)
nt (ra DIHP)	Rapidly Biodegradable (ra, ex1)
nt (ra DIHP)	>99 primary 90.3 ultimate (3) Rapidly Biodegradable

Table 3
Toxicology Data Summary
Phthalate Esters

nt (ra [illegible])	98 primary (10 days)
nt (ra DIHP)	Rapidly Biodegradable (ra, ex1)
nt 0.82 (12)	Rapidly Biodegradable (ra, ex1)
nt 1.05 (12)	70.5 (1) Rapidly Biodegradable
nt (ra DINP)	Rapidly Biodegradable (ra, ex1)
nt (ra DINP)	Rapidly Biodegradable (ra, ex1)
nt (ra DINP)	Rapidly Biodegradable (ra, ex1)
nt 1.0 (12)	67.1 (1) Rapidly Biodegradable
nt (ra DIDP)	57.4 (1) >99 primary 76 ultimate (3) Moderately Biodegradable
nt (ra DIDP)	Moderately Biodegradable (ra, ex2)
nt (ra DIDP)	Moderately Biodegradable (ra, ex2)
nt 0.9 (12)	12.8 (1) 62.7 (56 days) (1) >50 primary 37 ultimate (3) Moderately Biodegradable
nt (ra DTDP)	Moderately Biodegradable (ra, ex3)

Table 4
Physical/Chemical Data Summary
Phthalate Esters

Primary Carbon Chain Length(s)	CAS Number	Chemical Name	MP* (°C)	BP** (°C @1013 hPa)	VP (hPa @25°C)	PC (log Pow)	Water Solubility (mg/L @25°C)	Photodeg. Half-life*** (days)	Hydrolysis Half-life (yrs)	Trar	
										Soil	Air
Low Molecular Weight Phthalate Esters											
C1	131-11-3	dimethyl ester **(DMP)**	5.5	249 c	2.63E-03	1.61	5220	18.6	2.7	3.5	0.2
C2	84-66-2	diethyl ester **(DEP)**	-40	282 c	6.48E-04	2.54	591	3.1	2.9	23.3	0.4
Transitional Phthalate Esters											
C4, C6	85-68-7	butylbenzyl ester **(BBP)**	-35	387	2.49E-05	4.7	3.8	0.97 c	1.4 c	95.6	0.1
C6	68515-50-4	dihexyl ester branched & linear **(DHP)**	-27	373 c	3.45E-06	6	0.159	0.95 c	3.5 c	97.6	0
C6	84-75-3	di-n-hexyl ester **(DnHP)**	-27	385 c	3.45E-06	6	0.159	0.72 c	3.4 c	97.6	0
C7	68515-44-6	diheptyl ester branched & linear **(DinHP)**	-45	364 c	9.33E-07	6.87	0.02	0.57 c	4.2 c	97.7	0
C7	71888-89-6	di C6-8 branched **(DIHP)**	-45	394 c	9.33E-07	6.87	0.017	0.6 c	3.4 c	97.6	0.1
C8	27554-26-3	diisooctyl ester **(DIOP)**	-46	417 c	2.52E-07	7.73	2.49E-03	0.52 c	3.4 c	97.7	0
C7, C9	111381-89-6	C7,C9, branched & linear **(Din79P)**	-45	417 c	2.52E-07	7.73 c	2.49E-03 c	0.49 c	4.2 c	97.7	0
C7, C11	111381-90-9	C7, C11, branched & linear **(711P)**	<-50	440 c	6.80E-08	8.6	3.10E-04	0.43 c	4.2 c	97.7	0
C7, C12	16883-83-3	benzyl C8-oxybutyl **(B84P)**	-6.5	474 c	8.48E-09	7	1.47E-03	0.62 c	1.6 c	97.7	0
High Molecular Weight Phthalate Esters											
C6, C8, C10	68648-93-1	mixed decyl & hexyl and octyl esters **(610P)**	-45	431 c	1.33E-07	8.17	8.80E-04	0.52 c	7.7 c	97.7	0
C8	117-84-0	dioctyl ester **(DnOP)**	-25	431 c	1.33E-07	7.73	2.49E-03	0.52 c	7.7 c	97.7	0
C8	68515-40-2	benzyl C7-C9 branched & linear **(B79P)**	-48 to -35	427 c	5.79E-07 c	6.74 c	8.47E-03 c	0.64 c	1.4 c	97.7	0
C7, C9	68515-41-3	(C7-C9) branched & linear alkyl ester **(in79P)**	-48 to -45	424 c	9.24E-08	8.47	2.06E-04 c	0.52 c	4.7 c	97.7	0

Table 4
Physical/Chemical Data Summary
Phthalate Esters

C9	28553-12-0 68515-48-0	diisononyl ester **(DINP)**	-48	454 c	6.81E-08	8.6	3.08E-04	0.46 c	7.7 c	97.7	0
C9	68515-45-7	dinonyl ester branched & linear **(DNP)**	-48	454 c	6.81E-08	8.6	3.10E-04	0.46 c	7.7 c	97.7	0
C10	68515-43-5	di-C9-C11 branched & linear **(911P)**	-48 to -35	466 c	2.04E-8 c	10.39 c	2.09E-06 c	0.47 c	4.7 c	97.7	0
C10	84-77-5	didecyl ester **(DDP)**	-46	477 c	1.84E-08	9.46	3.81E-05	0.41 c	7.7 c	97.7	0
C10	26761-40-0 68515-49-1	diisodecyl ester **(DIDP)**	-46	454 c	1.84E-08	9.46	3.81E-05	0.56 c	3.4 c	97.7	0
C11	3648-20-2	diundecyl ester **(DUP)**	-9	501 c	4.97E-09	10.33	4.41E-06	0.37	7.7 c	97.7	0
C11	85507-79-5	di (C11) ester branched & linear **(DIUP)**	-9	498 c	4.97E-09	10.33	4.41E-06	0.33 c	6.3 c	97.7	0
C9, C11	111381-91-0	C9, C11, branched & linear **(Din911P)**	-50	456 c	1.01E-07 c	10.28 c	2.59E-06 c	0.38 c	4.2 c	97.5	0.2
C13	68515-47-9	di-C11-C14, C13 rich ester **(DTDP)**	-50	501 c	3.63E-10	12.06	7.00E-08	0.42 c	7.7 c	97.7	0

c = Calculated data using EPI SuiteTM.

* = All phthalate esters higher than DMP are liquids at zero degrees C. Mixtures are expected to have melting points below those of components. Modeled data do not accurately reflect melting poi

** = Many of the higher phthalate boiling points are determined under reduced pressure but have been extrapolated to one atmosphere.

*** = Based on a 12-hour day; the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated.

Highlighted substances are not in the High Production Volume Chemical Program but have data that are included to support the hazard evaluation of the phthalate ester category.

Table 4
Physical/Chemical Data Summary
Phthalate Esters

nsport (%) Level I EQC Model			
Water	Biota	Sediment	Suspended Sediment
96.2	0	0.1	0
75.8	0	0.5	0
2.2	0	2.1	0.1
0.1	0	2.2	0
0.1	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1

Table 4
Physical/Chemical Data Summary
Phthalate Esters

0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1
0	0	2.2	0.1

›ints for these substances.